AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR THE STUDY OF THE CIRCULATION

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American Heart Journal

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Original Communications

PULMONARY BLOOD DISTRIBUTION AND OXYGEN DIFFUSION IN MITRAL STENOSIS

NOBLE O. FOWLER, M.D., ROBERT CUBBERLY, M.D., AND EDWARD DORNEY, M.D.

NEW YORK, N. Y.

IN the normal resting human subject there is usually a higher oxygen tension in the pulmonary alveoli than in the systemic arterial blood. This was demonstrated by Lilienthal and co-workers.[1] This alveolar-arterial gradient was described as having two components.[1] One is a diffusion component, which is due to the resistance offered to the diffusion of oxygen by the pulmonary membrane, which is in turn composed of the capillary endothelium, the blood plasma, and the intracellular fluid and cell wall of the erythrocyte. The other component is that of venous admixture, which arises from venous blood which enters the systemic circulation without adequate exposure to alveolar air. This factor results from blood in the Thebesian and anterior cardiac veins entering the left ventricle, blood entering pulmonary veins from bronchial veins, and pulmonary capillary blood which passes through portions of the lung which are well perfused but poorly ventilated.

In 1951, Riley and associates[2] described a method for separating the alveolar-arterial oxygen tension gradient into its two components by studying the human subject at two different levels of oxygenation. The present paper describes studies made by this technique in thirteen patients with mitral stenosis while breathing air and then 13.78 per cent oxygen in nitrogen. In addition to the measurement of blood carbon dioxide and oxygen tensions, cardiac outputs were calculated and mitral valve areas were estimated. The response of the pulmonary arterial pressure to hypoxia was observed. The respiratory dead space and the oxygen diffusing capacity of the lungs were calculated. Also, comparisons were made between calculated pulmonary capillary effective oxygen tensions and tensions measured directly upon pulmonary "capillary" blood samples.

From the Cardiac Laboratory, Brooklyn Hospital, Brooklyn, N. Y., and the Department of Medicine, State University of New York, New York City.

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MATERIAL

The subjects studied comprised thirteen patients with mitral stenosis from the medical service of the Brooklyn Hospital. Their ages were from 14 to 48 years. Three had also mitral insufficiency, and one had aortic insufficiency.

METHODS

The studies were performed as described by Riley and associates.[2] An especial effort was made to secure a steady state during these studies. Patients were made familiar with the apparatus; moderate sedation was employed; pulse and respiratory rates were stabilized after placement of the cardiac catheter and arterial indwelling needle. All patients breathed air and then the 13.78 per cent oxygen mixture for at least 15 minutes before the collection of blood and expired air samples. The importance of the steady state in studies of this sort has been emphasized by Fishman and co-workers.[3]

Mixed venous blood samples were secured from the pulmonary artery. Oxygen consumptions were determined from analysis of 3-minute samples of expired gas, collected in Douglas bags, measured in a Tissot spirometer, and analyzed in a Scholander microgas analyzer. Duplicate samples were required to check within 0.04 volume per cent. Samples of arterial and mixed venous blood were obtained midway during the collection of expired gas, and analyzed in the Van Slyke apparatus for carbon dioxide and oxygen content. Arterial and pulmonary "capillary" blood samples were analyzed for carbon dioxide and oxygen tensions by the direct method of Riley and associates.[4] Pulmonary "capillary" pressures and blood samples were obtained in the manner of Hellems and co-workers.[5]

Pulmonary arterial and "capillary" pressures were recorded by the Sanborn Poly-Viso electrocardiograph and electromanometers. Mean pressures were obtained by planimetry. Arterial pH was measured by the Cambridge pH meter (research model). Cardiac outputs were calculated by the Fick principle. Mitral valve orifice areas were calculated by the hydraulic formula of Gorlin and Gorlin.[6]

Pulmonary capillary oxygen tensions, per cent of venous admixture, respiratory dead space, and oxygen diffusing capacity of the lungs were determined from the formulas and graphs of Riley and associates.[2]

RESULTS

The results are summarized in Tables I and II. In Table I, it may be seen that there was a significant rise (over 5 mm. Hg) during hypoxia of mean arterial pressure in the pulmonary artery in ten of the thirteen patients. The resting pulmonary "capillary" pressure was elevated or at the upper limit of normal in ten of the eleven subjects in whom the measurement was made.

It may be seen by reference to Table I that two subjects had pulmonary "capillary" mean pressures five millimeters of mercury higher than the end-diastolic pressure in the pulmonary artery. Although this may be due to technical error or to variation in the state of the patient, we have observed this discrepancy previously. In this connection, it may be pointed out that the diastolic

pressure in the pulmonary artery is measured at its brief nadir at the end of diastole, and that the pulmonary "capillary" pressure would exceed the pulmonary arterial diastolic pressure for only a few hundredths of a second. Also, the discrepancy in pressures between pulmonary "capillary" and pulmonary artery in diastole would probably be less if the comparison were made using the instantaneous pulmonary "capillary" pressure taken at the same time in the cardiac cycle as the pulmonary arterial diastolic pressure.

TABLE I

PATIENT N. Y. HEART CLASS.	R. Q.	OXYGEN CONS. C.C./MIN.	CARDIAC OUTPUT L./MIN.	PULM. ARTERIAL PRESSURE MM. HG MEAN: SYS./DIAS.	PULM. "CAP." MEAN PRESS. MM. HG	CALC. MITRAL VALVE AREA SQ. CM.
1. F.D. 40F M.S. IA	0.76 0.85	185 178	4.56 6.83	11: 17/9 15: 24/8	7	3.7
2. L.G. 26F M.S. IA	0.60 0.99	230 196	4.51 4.26	13: 24/9 15: 28/10	14	1.6
3. M.H.* 48F M.S. IIB	0.78 0.75	206 199	4.16 3.32	18: 29/13 28: 40/17	16	1.0
4. J.P. 14M M.S. IIB	0.77 0.82	216 188	4.80 5.22	18: 26/11 24: 39/14	13.5	1.4
5. C.Q. 36F M.S. IIB	0.74 0.835	149 146	2.10 2.45	19: 31/13 36: 44/28	15	0.5
6. G.G. 42M M.S. IIB	0.73 0.81	235 220	6.63 5.43	26: 38/20 40: 63/30	23	1.4
7. L.S. 27F M.S., M.I. IIC	0.77 0.85	256 244	6.57 6.78	30: 46/17 48: 74/29	22	1.6
8. T.R. 37M M.S., M.I. IIC	0.80 0.79	241 248	3.98 4.35	29: 46/17 51: 69/39	19	0.7
9. L.W. 31F M.S., M.I. A.I., IIIC	0.75 0.80	199 190	3.34 3.51	52: 85/34 60: 84/39	27	0.8
10. F.P. 36F MS, IIIC	0.88 0.86	194 191	4.68 5.03	49: 65/37 69: 89/57	25	0.8
11. J.L.† 37M, M.S. IIIC	0.80 0.77	282 302	6.14 5.92	61: 76/46 61: 81/50	31	1.0
12. M.N. 32F M.S., IIIC	0.71 0.77	185 160	2.59 2.58	56: 70/46 62: 77/49	—	—
13. G.L. 31F M.S. IVE	0.77 0.81	190 171	2.29 2.03	58: 83/47 74: 110/59	—	—

The upper of paired values represents an observation during the breathing of ambient air; the lower an observation during hypoxia.

*Values for arterial PCO_2 were calculated rather than measured.

†Studied while breathing ambient air and 24.57 per cent oxygen in nitrogen.

The changes during hypoxia were compared with the criteria of Fishman and associates[3] for the maintenance of a steady state. With regard to respiratory quotient, the criterion was met in twelve of the thirteen subjects (change not exceeding 0.11); with regard to oxygen consumption, the criterion was satisfied in ten of the thirteen subjects (change not exceeding 11 per cent); in the other three cases, the changes in oxygen consumption were only slightly in excess of this: 13 per cent; 13.5 per cent; and 15 per cent. The calculated mitral valve orifice areas were below normal (4 to 6 sq. cm.) in all instances but one, that of

TABLE II. RESPIRATORY DATA IN MITRAL STENOSIS

CASE NO.	EFF. ALV. O_2 TENS.	PULM. CAP. EFF. O_2 TENS.	ART. O_2 TENS.	ALV.-ART. GRAD.	VENOUS ADMIX. (%)	O_2 DIFF. CAPACITY C.C/MM./MIN./SQ. M.	RESP. DEAD SPACE C.C/SQ. M.	OBSERVED PULM. "CAP." O_2 TENSION
1.	97 54.5	97 60.5	90.6 58	6.4 −3.5	5 5	18.3	64	—
2.	104 78	104 77	96 72	8 6	4 4	10.9	48	103.3
3.	102.2 53.2	102 60	76 55	26.2 −1.8	11 11	Normal	144	—
4.	114.7 41.1	114 42	92.4 45.6	22.3 −4.5	8.5 8.5	Normal	129	—
5.	89.2 58.6	89.2 53	92.6 53	−3.4 5.6	0 0	6.2	122	112
6.	96.1 57.7	96 56	86 52.8	10.1 4.9	7 7	12.2	42	110
7.	96.7 56	97 53	90 51	6.7 5.0	3 3	13.1	53	95.5
8.	100 45.5	100 39	87 38	13 7.5	5 5	11	40	101
9.	90 53.3	90 49	77 45	13 8.3	6 6	8.4	61	110
10.	101.8 57	102 49	91 47	10.8 10	4 4	6.0	111	91.4
11.*	118.5 87.5	115 70	74 55	44.5 32.5	17 17	4.6	279	—
12.	92 38.5	92 38	74 37	18 1.5	8 8	Normal	42	—
13.	94.8 60.9	94 50.5	84 48.3	10.8 12.6	3.5 3.5	5.4	239	—

The upper of paired values represents an observation during the breathing of ambient air; the lower represents an observation during hypoxia.

*Studied while breathing ambient air and 24.57 per cent oxygen in nitrogen.

Tensions are expressed in mm. Hg partial pressure.

Diffusing capacity of the lungs is expressed as normal when the mean pulmonary alveolar-pulmonary capillary oxygen tension gradient is small.

an asymptomatic patient. In eight of the eleven cases, the valve orifice areas were in the range usually associated with limited cardiac reserve and were consistent with the clinical evaluation of the patient in all subjects save one (C. Q.).

In Table II are shown the results of the blood and gas tension studies. The alveolar-arterial oxygen tension gradient was increased (above 13 mm.) in four of the thirteen patients. In five cases there was an increase in the percentage of venous admixture (above 6 per cent). Two of these five patients did not exhibit resting pulmonary hypertension. Six patients had an increase in the respiratory dead space (above 100 c.c. per square meter). Three of these showed an increase in venous admixture. Five subjects demonstrated a decrease in the oxygen diffusing capacity of the lungs (below 9 c.c./min./mm. gradient/sq. meter). It is of interest that four of these had very high pulmonary arterial pressures; the other had a small calculated mitral valve orifice area. One of these subjects had also an increase in venous admixture.

The pulmonary "capillary" oxygen tensions measured by the direct method were very close to the calculated tensions in three of seven instances (within 1.5 mm.). In three instances the observed tensions were much greater than the calculated tensions, exceeding these values as well as the effective alveolar tensions by 23, 20, and 14 mm. In one instance, the measured pulmonary "capillary" tension was 11 mm. less than the calculated value.

DISCUSSION

In 1952, Blount and co-workers[7] described an increase in the alveolar-arterial oxygen tension gradient in some instances of mitral stenosis. These workers did not in this report attempt to study their patients at two different levels of oxygenation. Carroll and associates[8] published recently an extensive study of twenty-nine patients with mitral stenosis in which evaluation was made of venous admixture and alveolar-capillary diffusion. These workers did not measure cardiac outputs, arteriovenous oxygen differences, or arterial pH at the time of their tension studies, and many of their data are based upon assumptions with regard to these values. Carroll and co-workers believe that the presence of increased venous admixture in mitral stenosis could be correlated with the finding of pulmonary congestion, increased pulmonary "capillary" pressure, and a tendency toward pulmonary edema. In our group, the highest percentage of venous admixture (17) was associated with the highest pulmonary "capillary" pressure in a patient who had had pulmonary edema; however, increased venous admixture was also found in a patient (J. P.) who had minimal symptoms and a pulmonary "capillary" pressure at the upper limit of normal. Three of six subjects having increased respiratory dead space also had an increase in venous admixture. This is to be expected, since areas of lung which are ventilated but not perfused and vice versa will cause increase in both.

Four of the five instances of low oxygen diffusing capacity of the lungs were associated with the highest pulmonary arterial pressures in the group, and it may be that there is some association between this finding and pulmonary congestion. Carroll and co-workers,[8] however, thought that this abnormality was associated

with areas of pulmonary fibrosis and closure of pulmonary capillaries. The latter was thought to be the result of vasomotor action. In our group, abnormalities in oxygen diffusing capacity showed a closer association with the clinical picture of dyspnea and with pulmonary hypertension than did abnormalities in respiratory dead space or in venous admixture. In a recent study of ten subjects with mitral stenosis, eight of whom were catheterized, Blount and co-workers[9] found no correlation between impaired pulmonary oxygen diffusion and elevated pulmonary "capillary" pressure.

The observation of a significant increase in pulmonary arterial pressure during hypoxia in ten of thirteen subjects was somewhat surprising. Fishman observed this change much less often in his patients with chronic cardiopulmonary disease.[3] Since the cardiac output showed little or no increase during hypoxia in our study, it may be presumed that the observed elevation in pulmonary arterial pressure is due to pulmonary arterial constriction comparable to that seen in normal human beings[10] notwithstanding the fact that pulmonary "capillary" pressure was not measured during hypoxia in the present study. An alternative explanation of the elevation in pulmonary arterial pressure observed during hypoxia is that of left ventricular failure induced by hypoxia. This seems unlikely, since this does not occur in normal subjects with this degree of hypoxia, and the left ventricle was not enlarged in the majority of the patients studied.

The comparison between calculated pulmonary capillary oxygen tension and effective alveolar oxygen tension on the one hand, and directly measured pulmonary "capillary" oxygen tensions on the other, is of interest. Direct measurement of pulmonary "capillary" oxygen tension was possible in seven instances. It is difficult to obtain pulmonary "capillary" samples of sufficient size for tension measurement unless the pulmonary "capillary" pressure is somewhat elevated. It will be noted that the measured pulmonary "capillary" oxygen tension was greater than the directly measured arterial oxygen tension from the same patient in all instances, supporting the concept that the "capillary" samples are not appreciably contaminated by mixed venous blood from the pulmonary artery. In three instances the calculated and measured pulmonary capillary oxygen tensions were virtually identical. It seems likely that this is more than coincidental; however, further study of this problem is necessary.

In the other four instances, there was considerable discrepancy between the observed and calculated pulmonary capillary oxygen tensions. In one instance, the measured value was lower than the calculated value. Possible explanations for this difference are failure to maintain a steady state; slight contamination of the sample by mixed venous blood; relatively poor ventilation of the area of lung from which the sample was taken. The steady state seemed well maintained in this patient; one of the other two possibilities seems more likely. In the other three instances of discrepancy, the measured oxygen tension of pulmonary "capillary" blood was much higher than either the calculated value of capillary oxygen tension or than the calculated value for effective alveolar oxygen tension. Possible explanations for this are failure to maintain a steady state, better ventilation of the area of lung from which the sample was drawn than of the lung as a whole, and secretion of oxygen by the alveoli. Better ventilation of the areas of

lung from which the samples were drawn seems most likely; this is supported by the fact that carbon dioxide tensions were considerably lower than the corresponding arterial carbon dioxide tensions in these pulmonary "capillary" blood samples. This problem is being studied further.

SUMMARY

1. In thirteen patients with mitral stenosis, a study was made of the relative contributions of venous admixture and pulmonary oxygen diffusing capacity to the alveolar-arterial oxygen tension gradient.

2. In this group, five subjects had an increase in venous admixture, and six had an increase in respiratory dead space. Of those with increase in dead space, three had an increase in venous admixture. These abnormalities did not show good association with the clinical state of the patient, or with the height of the pulmonary vascular pressures at rest.

3. Five subjects demonstrated a diminution in the oxygen diffusing capacity of the lungs. Four of these were dyspneic and had high pulmonary vascular pressures. One had a very small calculated mitral valve orifice area with little elevation in pulmonary arterial pressure at rest.

4. Direct measurement of pulmonary "capillary" oxygen tension was made in seven subjects. In three there was good agreement with the calculated pulmonary capillary tension. Possible explanations for the discrepancy in the other four cases are given.

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COMPARISON OF THE OXYGEN TENSION IN BLOOD FROM THE LEFT ATRIUM AND A SYSTEMIC ARTERY

VIKING OLOV BJÖRK, M.D., GUNNAR MALMSTRÖM, M.D., AND LARS-GUSTAF UGGLA, M.D.

STOCKHOLM, SWEDEN

IN cases with diseased mitral valves the enlarged left atrium has been reached by direct paravertebral puncture from the right side according to Björk and co-workers.[1] As a 20 cm.-long, wide-bore needle with 1.0 mm. inside diameter manufactured by Stille-Werner, Stockholm, is used, a blood sample is easily obtained. The oxygen tension in blood from the left atrium may then be compared with the oxygen tension in simultaneously obtained samples from a systemic artery as well as from the "pulmonary capillaries." The decreased oxygen tension in the systemic artery as compared to the oxygen tension in the left atrium may be considered as an expression of the admixture of venous blood from the Thebesian veins emptying in the left ventricle (provided a congenital malformation and abnormal anastomoses can be excluded).

The decrease in oxygen tension of the blood between the "pulmonary capillaries" and the left atrium probably is mainly due to the bronchial veins. An uneven ventilation and an impaired diffusion of oxygen from the alveoli to the blood in cases with mitral disease and pulmonary hypertension may also decrease the oxygen tension. The longer equilibration time between alveoli and the capillaries, when blood is withdrawn from the "pulmonary capillaries," may tend to increase the oxygen tension in these samples.

METHOD

During heart catheterization of patients with mitral valvular disease, the left atrium has been punctured according to Björk. Blood samples then have been taken simultaneously from the left atrium, a systemic artery (the brachial artery was used in all but one case where the femoral artery was punctured) and from the "pulmonary capillaries."

Four milliliters of blood have been withdrawn into 10-ml. glass syringes previously flushed with 5 per cent heparin. No fluoride has been used. In order to avoid glycolysis the analyses of the oxygen tension have been performed immediately according to the method of Riley and associates[3] with the modification by Björk and Hilty.[2] The error of the method has been computed from the

From the Sabbatsberg Hospital, Surgeon-in-chief: C. Crafoord, M.D., Professor; Physicians-in-chief: S. Björkman, M.D., and S. Åkesson, M.D., and the Clinical-physiological Laboratory of the Serafimer Hospital, Stockholm, Sweden.

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difference between the double analyses in 37 cases. No significant difference was found between the first and second determination. (The error of the method was calculated to ±0.13 mm. Hg when a single determination was performed.) The coefficient of variance was 1.2 per cent (Table I).

TABLE I. ERROR OF METHOD FOR OXYGEN TENSION ESTIMATION CALCULATED FROM DOUBLE DETERMINATIONS

NO. DOUBLE DETERMINATIONS	DIFFERENCE pO_2 SAMPLE I—pO_2 SAMPLE II				
	Mean	S.D.	Range	d	V
37	−0.03 ± 0.18	±1.07	+2 −3	±0.13	1.2%

Values in mm. Hg. S.D. = Standard deviation of the difference. d = Standard error of a single determination. V = Coefficient of variance.

MATERIAL

Eleven patients with mitral valvular disease and without signs of congenital cardiovascular malformations have been investigated. The patients have been invalidized from their disease. Eight patients were compensated at rest while two patients had an elevated pressure at rest in the right atrium (Table II).

RESULTS

The oxygen tension was found to be on an average 7.5 mm. Hg higher in the left atrium as compared to the systemic artery. This difference was found to be statistically significant ($P < 0.001$).

The oxygen tension in a blood sample drawn from the heart catheter in the "pulmonary capillary" position was found to be on an average 21.1 mm. Hg higher than in blood from the left atrium. This difference was statistically significant ($P < 0.001$).

The decrease in oxygen tension between the "pulmonary capillaries" and the left atrium was found to be more pronounced than the decrease of oxygen tension between the left atrium and a systemic artery ($0.01 > P > 0.001$).

DISCUSSION

The higher oxygen tension in the left atrium as compared to that in a systemic artery is mainly due to an admixture of venous blood from the left ventricular myocardium provided a congenital malformation with a right-to-left shunt and venous admixture through anomalous venous anastomoses can be excluded.

(1) The amount of blood draining into the left ventricle through the Thebesian veins per unit of time, and (2) the oxygen content of this venous blood will influence the decrease of oxygen tension in the arterial blood. Both factors will vary in different individuals as well as in the same individual on different occasions. The arteriovenous oxygen difference is known to be high

TABLE II. OXYGEN TENSION IN SIMULTANEOUSLY OBTAINED BLOOD FROM "PULMONARY CAPILLARIES" (PC), LEFT ATRIUM (LA), AND SYSTEMIC ARTERY (SA)

CASE	CLINICAL DIAGNOSIS	OXYGEN TENSION VALUES				MEAN PRESSURE			S/D PRESSURE	HEART VOLUME ML.
		PC	LA	SA	DIFF. LA-SA	LA	RA	PA	BA	
1.	Mitral stenosis	122 123	93 94	81	+12.5	9	7	28	115/60	1020
2.	Mitral stenosis with slight regurgitation	96 96	85 85	73 74	11.5	14	4	22	150/80	710
3.	Mitral stenosis	98 98	79 78	68 71	9.0	3	0	23	150/90	840
4.	Mitral stenosis		89 88	87	1.5	8	1	14	115/65	760
5.	Mitral stenosis	112 111	70 69	62	7.5	9	1	33	125/75	770
6.	Mitral stenosis with regurgitation	112 112	98 97	83 83	14.5	20	4	33	110/60	790
7.	Mitral stenosis with regurgitation	100 101	83 84	78 77	6.0	20	−5	39	175/95	1200
8.	Mitral stenosis		70 70	70 73	−1.5	10	−3	55	140/95	1440
9.	Mitral stenosis	105 106	80 78	68 67	11.5	28	10	41	120/75	1240
10.	Mitral stenosis	100 100	76 76	72 72	4.0	8	—	25	130/95	1020
11.	Mitral stenosis	95 93	77 79	72 72	6.0					

Values are given in mm. Hg. Pressures in mm. Hg are given for the left atrium (LA), the right atrium (RA), the pulmonary artery (PA), and the brachial artery (BA).

TABLE III

PO_2 DIFF. IN mm. Hg	MEAN	S.D.	RANGE	P
I PC −LA	21.1 ± 3.6	10.8	+42 +6	P<0.001
II LA −SA	7.5 ± 1.5	4.9	+14.5 −1.5	P<0.001

I = Difference of oxygen tension in blood from "pulmonary capillaries" and the left atrium = PC-LA in mm. Hg. S.D. = Standard deviation. II = Difference of oxygen tension in blood from the left atrium and a systemic artery = LA-SA in mm. Hg.

The difference between the differences I-II = 21.1 − 7.5 = 13.6 ± 3.9 mm. Hg ($0.01 > P > 0.001$).

in the myocardium of normal individuals. This is probably true also in cases with mitral valvular disease. Therefore, only a comparatively small amount of blood draining through the Thebesian veins into the left ventricle will result in a significant lowering of the oxygen tension.

The blood of the left atrium may not be completely mixed. The bronchial veins are mainly draining into the pulmonary veins but may occasionally be found to empty directly into the left atrium. Furthermore there may be uneven ventilation in different parts of the lungs. We do not believe these factors are responsible for the significant decrease of the oxygen tension of blood in the left atrium as compared to that in a systemic artery. An incomplete mixing in the left atrium may, however, be a source of error influencing the size of the decreased oxygen tension in some cases.

The existence of a right-to-left shunt may be excluded as there are no signs of such a malformation.

The difference in oxygen tension between blood from the left atrium and a systemic artery shows a considerable variation from +14 to −1.5 mm. Hg. The last value does not significantly differ from zero (±1.07) and might represent an error of the analyses. The difference seems to be greater in the four cases (1, 2, 6, and 9) with the highest pressure in the right atrium. This material is, however, too small to permit any definite conclusions. No correlation between the pressures in the left atrium, the pulmonary or brachial artery, of the heart volume, and the difference in oxygen tension between the left atrium and the systemic artery has been found. The pressure measurements in the systemic artery and in the right side of the heart have not been performed simultaneously with the withdrawal of blood samples. Nor have we performed simultaneous pressure measurements and withdrawal of blood from the coronary sinus.

The oxygen tension in blood from the "pulmonary capillaries" is considerably higher than in simultaneously obtained blood from the left atrium. This difference in oxygen tension is considerably greater than the corresponding difference between blood in the left atrium and in a systemic artery ($0.01 > P > 0.001$).

The withdrawal of 4 ml. of blood from the "pulmonary capillaries" takes usually 1 to 2 minutes. This blood is then slowly returning through the "pulmonary capillaries" resulting in a prolonged equilibration with the alveolar gases.

In cases with mitral stenosis, pulmonary hypertension, and changes in the pulmonary vascular bed such a prolonged equilibration time will probably increase the oxygen uptake.

The admixture of blood from the bronchial veins and possibly venous admixture through abnormal venous anastomoses from the mediastinum are probably responsible for the decrease of oxygen tension in blood from the left atrium as compared to the "pulmonary capillaries." An uneven ventilation may also play some part in decreasing the oxygen tension in the left atrium.

CONCLUSION

In patients with mitral valvular disease the oxygen tension in blood from the left atrium was found to be significantly higher than that in a systemic artery. This difference might be due to an admixture of venous blood from the Thebesian veins in the left ventricle.

SUMMARY

1. The oxygen tension has been estimated in blood simultaneously collected from the left atrium, a systemic artery, and from the "pulmonary capillaries" in eleven patients with mitral valvular disease.

2. The oxygen tension is on an average higher in the "pulmonary capillaries" as compared to the left atrium and higher in the left atrium than in a systemic artery. These differences are statistically significant.

3. The difference in oxygen tension between blood from the "pulmonary capillaries" and the left atrium is larger than the difference between the left atrium and a systemic artery.

4. The explanations for these differences in oxygen tension are discussed.

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SPREAD OF ACTIVATION IN THE LEFT VENTRICULAR WALL OF THE DOG. III.

Transmural and Intramural Analysis

D. Durrer, M.D., L. H. van der Tweel, M.S., and J. R. Blickman, M.D.

Amsterdam, Holland

INTRODUCTION

A COMPARISON is made between the transmural wall curve (electrodes at either side of the wall) and the normal unipolar epicardial and cavity curves.

To obtain a closer analysis, electrode needles are introduced into the ventricular wall and all kinds of registration from the leadpoints of this needle, mutually, and with respect to the cavity and periphery are made.

The results of these experiments led us to assume that the inner layers are activated more or less synchronously and that the outer layers are activated successively by muscle conduction. The synchronicity of the inner layers is caused by the Purkinje system that penetrates in the ventricular wall for about two-fifths of the thickness of the wall. In the transition zone between synchronously and successively activated layers a muscle layer is sometimes found in which the activation spreads from epicardium to endocardium.

In a greater part of the ventricular wall, deep negative ventricular complexes are found in the unipolar leads. The epicardial lead has a small voltage compared with the intramural complexes of the ventricular wall involved. This type of lead does not reflect that part of the depolarization process occurring in the inner layers of the ventricular wall.

TERMINOLOGY

Although described fully in the text we think it necessary for a better understanding to give a short survey of the terminology. The electrode position for each type of curve is as follows:

1. *Transmural wall curve:* One electrode in the cavity, the other one at the epicardial surface. The connecting line of these electrodes is perpendicular to both surfaces. The electrodes are lying close together at opposite sides of the wall.

2. *Partial wall curve:* One electrode in the cavity, the other one lying in the ventricular wall on the line perpendicular to both surfaces.

From the University of Amsterdam, Holland, Department of Internal Medicine, Wilhelmina Gasthuis, Director: Prof. Dr. P. Formijne, Laboratory for Medical Physics.

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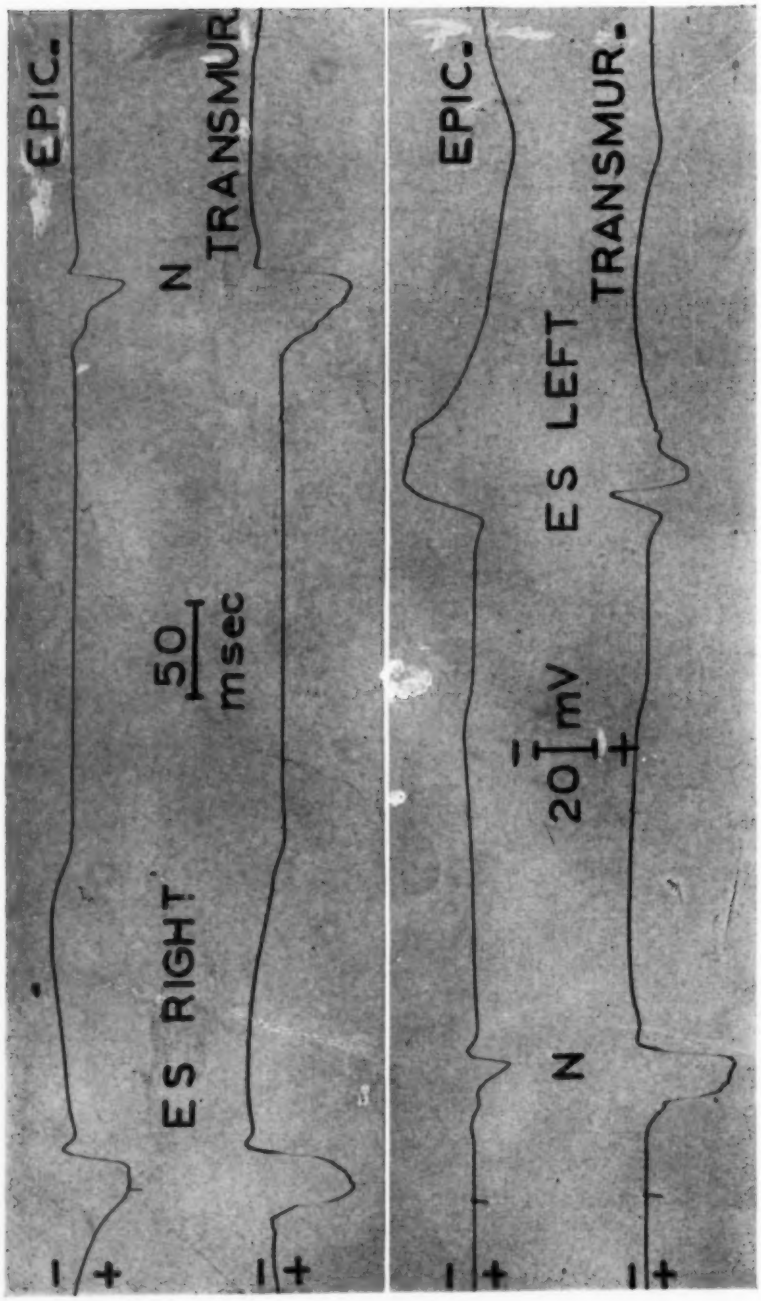

Fig. 1.—Note the polarity of the curves. The upper tracing in both rows is a unipolar epicardial lead from the left ventricular wall; the lower tracing is the corresponding transmural wall curve.

Upper row. The first complex in both leads is an extrasystole (ES right), caused by mechanical stimulation of a point on the right ventricular surface. The wall curve of this extrasystole does not differ much from the wall curve of the normal beat. The smooth positive deflection in the first part of the epicardial complex of the extrasystole, caused by the activation of the septum from right to left, is not reflected in the wall curve. This means that both transmurally placed electrodes are equally positive during this part of the activation.

Lower row. Here a part of the left ventricular surface was stimulated (ES left). The form of the wall curve changes profoundly. The epicardial complex is broader than the wall curve: the activation of the latest activated part (right ventricle) has equal influence on both electrodes of the transmural lead.

3. *Unipolar epicardial curve:* The electrode is situated on the epicardial surface; the reference is on the left hind leg.

4. *Unipolar intramural curve:* The exploring electrode is situated in the ventricular wall; the reference electrode is the same as before.

5. *Unipolar cavity curve:* Here the exploring electrode is situated in the cavity.

6. *Bipolar Intramural curve:* The electrodes are situated in the left ventricular wall.

7. *Intramural differential curve:* The electrodes with a very short distance (0.2 mm.) are lying in the wall.

8. *Leadpoints:* The electrodes mounted in a needle-electrode are called leadpoints.

The leads will be numbered successively in the order of the relation of their position to that of the endocardium. When an 8-electrode needle is used, the leadpoint 8 will be the electrode that lies closest to the epicardium, and when a 12-electrode needle is used, leadpoint 12 will be closest to the epicardium.

TRANSMURAL LEADS

A recording with a unipolar lead is more or less influenced by all electrical phenomena taking place in the medium. The electrical processes close to the exploring electrode will have the greatest influence. With an epicardial lead this means that while the tracing reflects influences from the whole heart, the part of the muscle lying under this electrode plays a dominant role. Wilson and associates[1a,1b,2] pointed out that for the interpretation of the epicardial electrocardiogram it is very important to be informed as to the course of the cavity potential under the muscle region being examined. Wilson considered the geometrical conditions in the heart to be such that two transmurally placed electrodes are approximately similarly influenced by the activation of the more remote regions of the ventricular muscle. When a part of the left ventricular wall was infarcted, the epicardial and cavity curves of this region show nearly the same course. This fact was proved for the exposed heart but one could expect that when the heart is situated in a continuous conducting medium there is still an influence of activation in distant regions on the transmural curve. Also, proof was not given for the intact heart. In most of our experiments on the exposed heart of the dog the epicardium from which the leads were taken was relatively isolated from the surroundings. We do not know whether covering the epicardial surface with pads of cotton soaked in saline simulates sufficiently a continuous medium. It could, however, be shown that the transmural lead was little influenced by more distant regions of the heart. This influence could be lessened still further by an appropriate choice of the electrode positions. The electrodes were placed at the lateral side of the left ventricle in such a way that the line joining them was more or less perpendicular to the septum. Moreover, for these transmural leads a region was always chosen in which the epicardial complexes did not change much, when the area was explored with a small-tipped electrode, so that a regular front could be assumed to be present there. It was found that the shape of the wall curve during premature beats (extrasystoles) from the heterolateral, i.e., right, ventricle did not differ much from that in normal beats (Fig. 1). It is possible, however, to get changes in the wall curve.

On stimulation of a point on the surface of the left ventricle, a premature beat with changes in shape and polarity of the transmural wall curve is seen,

pointing to activation in endocardial direction of that part of the wall. In a few cases we found very small complexes which indicate a predominantly tangential course of the activation from that part of the wall.

Shape of the Transmural Wall Curve.—This curve consists as a rule of a broad positive wave, which is markedly asymmetrical (Fig. 2). The ascending limb is practically always slightly irregular. There is usually a rather broad

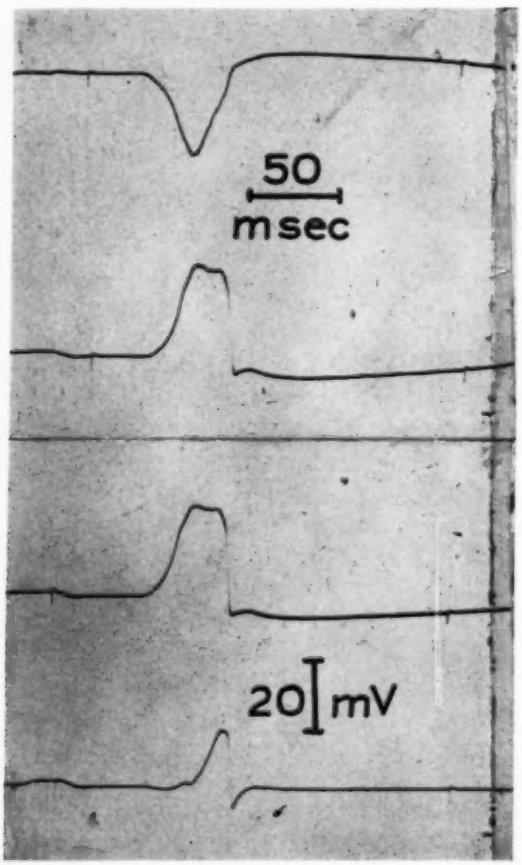

Fig. 2.—The uppermost tracing is a unipolar lead from the cavity, the second and third tracings are identical transmural wall curves from the same part of the ventricular wall, the lower tracing is the unipolar epicardial lead. The cavity curve is symmetrical, the wall curve asymmetrical. Note the very broad maximum and the steep part in the descending limb of the latter. This steep part is synchronic with the rapid part in the intrinsic deflection of the epicardial lead and has the same length. The nearly symmetrical course of the first part of wall and cavity curves is reflected in the nearly horizontal course of the first part of the epicardial lead. The epicardial curve shows a smaller voltage and a shorter duration than the other curves.

maximum sometimes with small irregularities. The descending limb consists of two parts: a slower part directly after the broad maximum, followed by a very fast part of precipitous character. This shape can be accounted for by the assumption that the activation front in the ventricular wall makes a small angle with the epicardium and propagates mainly in an apicobasal direction.

Relation Between Transmural Wall Curve and Epicardial Curve.—The properties of an epicardial curve can be better understood when the transmural wall curve for the same region is registered simultaneously. The wall curve is broader than the epicardial curve and of a higher voltage. The epicardial R wave is preceded by a few small irregularities which fall on the ascending limb of the wall curve. The beginning of the R wave itself occurs at a point near the maximum of the wall curve. The top of the R wave coincides with the "plateau" of the wall curve directly before the steeply descending part. In the first part of the epicardial curve, the large potential difference between the endo- and epicardial sides, caused by the activation of this part of the heart wall, is represented only by some small irregularities in the base line. In both parts the P waves are recognizable. The P-R interval is approximately 15 milliseconds shorter in the wall curve than in the corresponding epicardial curve. We found a time difference in all curves registered in this way.

The shape of the cavity curve is nearly symmetrical. The slope of the first part of the descending limb of the cavity curve does not differ much from the ascending part of the transmural curve. Sometimes, as in Fig. 2, the slope of the beginning of both curves is practically the same. In this case the corresponding part of the epicardial curve shows only small irregularities in the base line. Then the unipolar epicardial lead does not reflect that part of the depolarization process occurring in the inner layers of the left ventricular wall. Only after the nadir of the cavity curve occurs does the positive influence of the wall curve predominate, and this results in the R wave in the epicardial lead. The fast parts of the wall curve and the epicardial curve are identical. The cavity potential changes very little during the short time this fast part makes its appearance. When the activation of the wall has come to an end, the cavity potential predominates again.

Potential of Left Ventricular Cavity.—The potential of the left ventricular cavity is caused almost exclusively by activation of the free wall of the left ventricle and of the septum. The contribution of the papillary muscles is negligible. The cavity potential is not the same at all places in the cavity. At the apex, for instance, a small R wave and a deep S wave are sometimes found, and in the other parts of the cavity Q-S complexes of varying depths. These differences are due to differences in the potential contributions of the septum and ventricular wall for these places.

Influence of the Activity of the Septum on the Transmural Lead.—A long 12-electrode needle was introduced through the free wall into the left ventricle and septum until the leadpoint at the tip of the electrode was lying in the cavity of the right ventricle. With this position of the needle, several leadpoints were situated in the septum and in the cavity of the left ventricle, with some even in the free wall of the left ventricle (Fig. 3). The action curve registered between two leadpoints situated on either side of the septum (Fig. 4, transseptal curve, upper row) has a voltage of about one-third to one-half of the largest deflection in the cavity curve. The curve shows a flattened peak and its duration is the same as that of the cavity curve. The polarity of the complex points to an overall course of the activation process from left to right.

When extrasystoles are induced from the middle part of the right ventricle (Fig. 4, lower row), transseptal complexes are produced which have reversed polarity with respect to normal beats. The transmural curve becomes somewhat broader, the form of the complex remains unaltered. Stimulation of a point on the left ventricle (Fig. 4, middle row) does not reverse the polarity of the transseptal curve, but changes the transmural curve totally. These facts prove that activation of the septum in right-to-left direction and also in reversed direction influences both transmural electrodes in nearly the same manner.

In Fig. 4, small typical complexes are seen preceding the larger ones. They occur in the leadpoints situated in the innermost layer of the ventricular wall, close to the endocardium. Their time relations suggest that they are caused by activation currents in the Purkinje system.

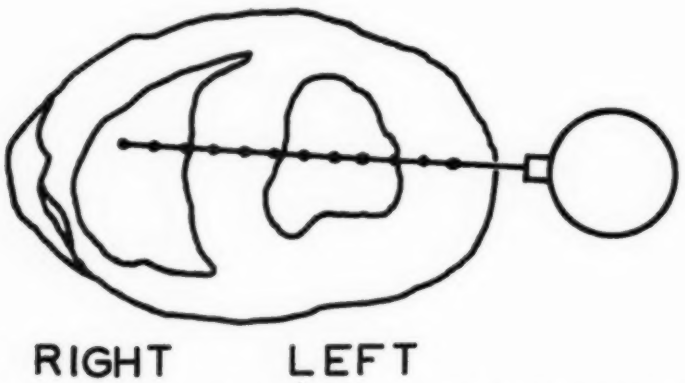

Fig. 3.—A long 12-electrode needle was introduced through the left ventricular wall, cavity, and septum, till the point of the needle was lying in the right ventricular cavity. The transeptal curve was registered between one leadpoint, lying close to the right side, and another, lying close to the left side of the septum.

Causes of the More or Less Similar Course of the Transmural Wall and Cavity Curves.—It is now possible to give a schematic explanation of the fact that the wall and cavity curves show a more or less similar, sometimes even an identical course with the first part. The cavity potential comprises contributions from the free wall and from the septum. The transmural potential difference is almost exclusively dependent on the activation of the wall, because both transmural electrodes are influenced in a practically identical manner by septum activation. Of these transmural electrodes, the cavity electrode is situated at the negative side and the epicardial electrode at the positive side of the intramural activation wave. As a result of this, the transmural potential is larger than that part of the cavity potential that is caused by activation of the wall. The cavity potential, of course, is registered with respect to a peripheral electrode. Thus, if there were no activation of the septum, the cavity potential at any moment would be smaller than the transmural potential. This difference would be smallest at the beginning of the activation of the wall because the endocardial electrode is then closest to the activation front and this relatively remote from the epicardial electrode which would then behave approximately as though it were a peripheral electrode.

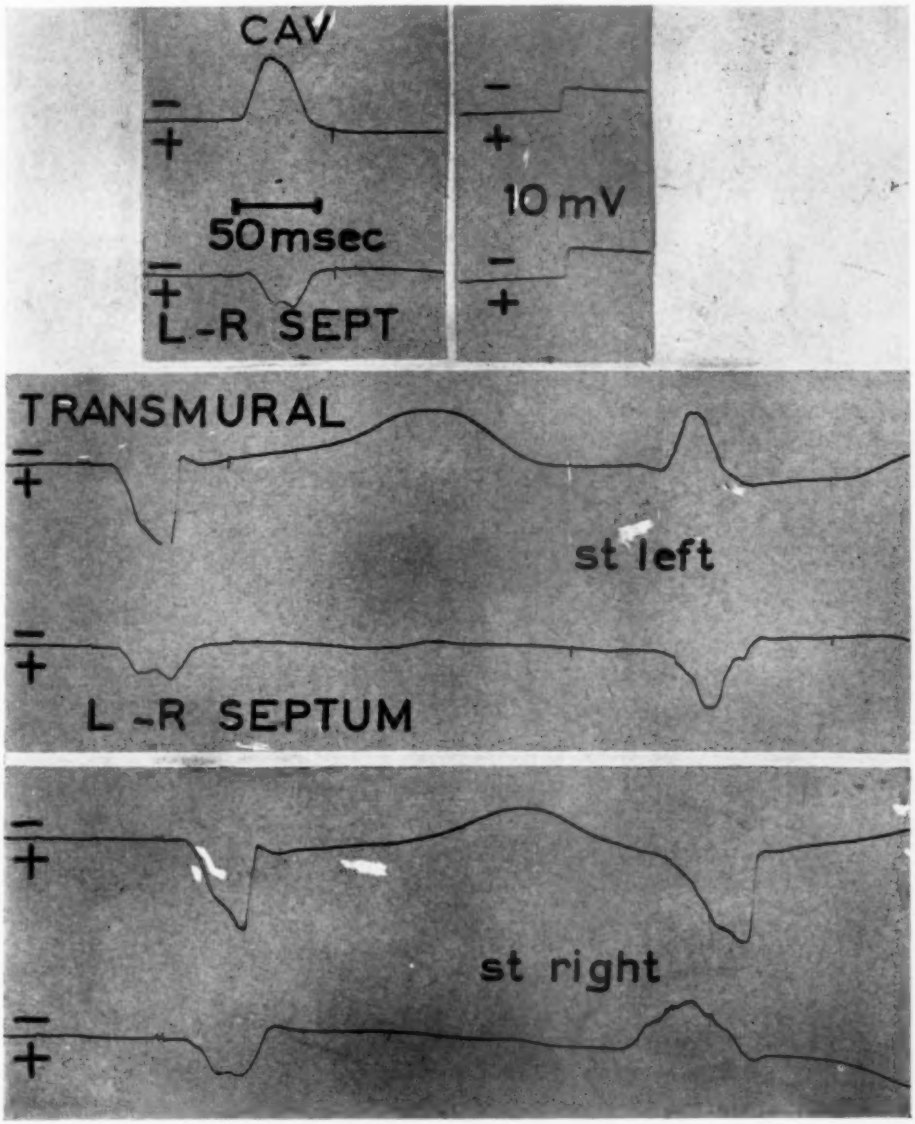

Fig. 4.—Upper row. The upper complex is the unipolar lead from the cavity. The lower complex is the transseptal lead, registered between two electrodes placed at both sides of the septum. Both complexes have the same duration. Note the broad maximum of the transseptal curve.

Middle row. A point of the left ventricular wall was mechanically stimulated (st. left). The transmural curve changes its polarity. The polarity of the transseptal curve does not change.

Lower row. A point on the right ventricular surface was stimulated (st. right). Now the polarity of the transseptal curve reverses. The transmural curve is slightly broader than during a normal beat; the form is nearly equal. Activation of the septum influences both transmurally placed leads in an approximately equal manner.

Note the small complexes approximately 10 milliseconds before the transmural and transsepta curves. It is probable that these are action currents of the Purkinje system.

The difference between the first parts of the cavity and transmural potentials is lessened by the influence of the activation of the septum, which causes a greater negativity of the cavity. It depends on various factors, such as the position of the electrode in the cavity and the distance from the septum, whether the first parts of the cavity and wall curves will be more or less nearly identical. Since the septum activity in the cavity curve near the free wall of the left ventricle always has a smaller influence than the wall activation, the first parts of the cavity and wall curves will always have a relatively high degree of similarity. This means that the first part of the epicardial curve will never show more than small potential differences with respect to the base line.

Although it is important to know the shape of the transmural curve, such a curve does not give a complete and undistorted picture of the activation process taking place in that part of the wall between the electrodes. This is due to the fact that small variations in the course of the activation in a small part of the muscle layer, situated between the electrodes, are not necessarily manifested as such in the transmural curve. For instance, a "reversal" phenomenon, occurring in some places of the heart wall, will be described in which the activation curves are mirror images. Therefore, the influence of these two layers on the shape of the wall curve is nil.

The electrical activity of remote muscle regions also influences the transmural curve to a certain degree, depending on the electrical-geometrical conditions. It is possible to make an approximation for this if one assumes that the electrical processes are occurring in a homogenous conducting medium. Even if all these factors are taken into account, only a rough picture of the intramural activation conditions can be made.

Experiments With Electrode Needles.—In our first experiments, thin electrodes were inserted in a row into the wall of the heart. It was found, however, that the spatial relationships between these electrodes varied greatly owing to the movements of the heart. When all the electrodes were joined together, a rather thick bundle was obtained which caused an extensive lesion, as a result of which marked changes in the electrical phenomena in the region examined were caused by their introduction into the heart wall. The multiple needle electrode provided a solution of these problems.[3]

Effects of contraction on position of the needle electrode: We shall now discuss the effect of the contractions of the heart on the position of the needle electrodes and see whether reliable results can be obtained in this manner.

Wiggers[4] in a recent publication states that the heart is electrically activated before any considerable change of shape has taken place: the electrical systole precedes the mechanical systole. The time interval between the beginning of the electrical phenomena and the beginning of the rise of pressure in the ventricle is 10 to 35 milliseconds.[5]

Eyster and associates[6] found that the beginning of the contraction of any small group of muscle fibers at the epicardial surface coincides with the peak of the differential action curves of the same fibers. Wiggers is of the opinion that the contraction of these small muscle groups falls within the phase during which the intraventricular pressure gradually rises, i.e., the isometric phase. Thus

the QRS complex is registered before appreciable changes in shape of the heart have occurred. There will certainly be some change of shape, as the heart approaches the spherical form during this phase. Volumetric measurements indicate that these changes are very small, not exceeding a few milliliters.[3] Larger changes are to be expected during the phase of ejection, but not in the first part of this because the amount of blood then ejected is very small and the semilunar valves open only slowly.

Rushmer and Thal[7] made an accurate analysis of the changes in thickness of the left ventricular wall by a cinematographic method. The internal radius of the left ventricular cavity in diastole (r_D) was taken as a standard of comparison. The external radius of the ventricle in diastole was found to be approximately 1.3 r_D; the thickness of the wall was 0.3 r_D. They found a decrease of both diameters during systole; the internal radius (r_D) became 0.6 of its original value (i.e., a decrease of the radius by 0.4); the external radius was reduced to 1.03 r_D. Thus the decrease of the external radius during systole was 0.27 r_D. The thickness of the wall during systole increased by about 0.13 r_D. With our method the base of the needle is fixed at the epicardial surface and makes the same movements. We may, therefore, conclude that the endocardial muscle layers will move over a fairly large distance (approximately 3 to 4 mm.) along that part of the needle lying in and near the cavity.

The S-T interval, which occurs during the "contracted state" of the heart muscle, is produced at the various leadpoints by muscle fibers, which during the QRS complex have communicated their electrical activity to leadpoints lying nearer to the epicardium.

Fixation of the needle electrodes: It was found that artifacts caused by the movements of the heart could be prevented by introducing the needle so far into the wall that the top of the needle electrode was lying free in the cavity, even during systole. The length of the needle must be such, that in this position the broad attachments for the connecting wires is resting on the epicardial surface. The surface of the needle must be very smooth, otherwise artifacts are caused by friction of the inner layers along the needle.

It was found possible to improve the fixation of the electrode needles in a simple way. The afferent wires were not led into the field of operation through the operation opening, but through a hole in the intercostal space below or above the field of operation. The opening made in this way gave sufficient possibilities for fixation of the wires. Finally, cotton wool pledgets soaked in saline were packed around the electrodes for further fixation.

It has been found that during experiments lasting many hours the shape of the complexes registered at the various leadpoints remains constant. Even with leads from two electrode needles set at some distance from each other in the heart wall, the complexes registered from the inner layers, sometimes very irregular in shape, remain constant for some hours (Fig. 5).

With differential needle electrodes in the inner layers we sometimes registered very irregular fast complexes. These also remained constant over long periods. This shows that the mechanism of the heartbeat remains remarkably constant for long periods of time, and that, apart from minor variations, the same muscle regions are situated at the same leadpoints during each heartbeat.

The experiments with differential needle electrodes are of great importance for the determination of the extent of the region injured by the insertion of the needle. If comparatively large sectors were disturbed by the lesion, there would be no large deflections in the corresponding differential leads, because of the fact that these differential leads only register phenomena in the immediately surrounding muscle parts.

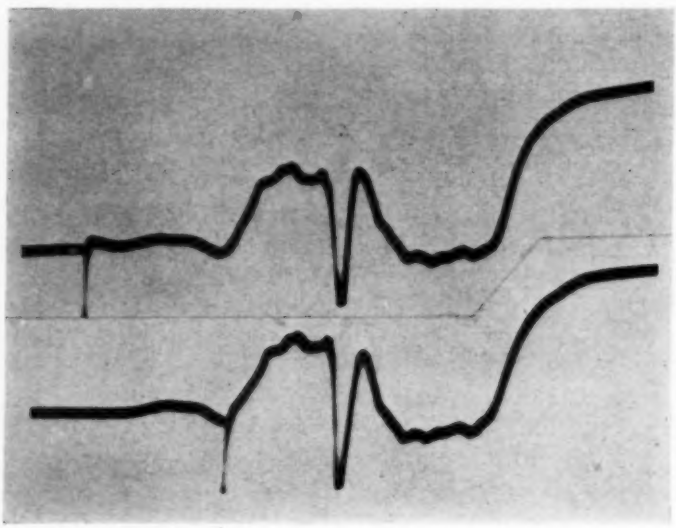

Fig. 5.—The complexes were registered between two leadpoints of 2 different needle electrodes, introduced in the left ventricular wall. The leadpoints were lying in the inner layers. The time interval between the registration of the upper and lower complex was approximately 2 hours. Note the close similarity of both curves. The spike in both curves is a time-mark.

EXPERIMENTS WITH NEEDLE ELECTRODES

Introduction of the Needle Electrode.—The needles were always introduced perpendicularly to the epicardial surface and then cautiously pushed in until the point was touching the endocardium (the resistance of the endocardium could be overcome by slight pressure). The insertion of the electrodes caused a few extrasystoles; ventricular fibrillation never occurred. In many cases it was extremely difficult to find the right place for the needles, the reason being that it is impossible to ascertain the position of the papillary muscles from the outside. Interference from the papillary muscles was least when the electrode was introduced in the region of the ventricular wall between them. Therefore, we, used mainly the lateral wall of the left ventricle for these experiments. Sometimes we had to make ten to fifteen attempts before we could find a place where the leadpoints at the tip of the needle lay free in the cavity. That the needle had been pushed through the papillary muscle was shown by the fact that cavity potentials were not observed. The success of the experiment depends on a correct placing of the needles. In all cases in which the position of the needles could be checked after the experiment, we found them to be lying free of the papillary muscles, which we had already concluded from the form of the curves.

After the introduction of the electrode, an injury effect was usually visible. The complexes then did not show any fast components. The fast components gradually reappeared; after 10 to 15 minutes the pronounced injury effect had practically disappeared. After this, all fast deflections remained until the end of the experiment, sometimes even when the heart was beating only once in 30 seconds.

In the first experiments a long needle was used. As the heaviest part of the needle electrode, i.e., the small box containing the connections, was far from the epicardium, the needle tended to make large movements as a result of which strong forces were exerted in the puncture canal, giving rise to marked injury effects. One of the first essentials to avoid this is, therefore, as described above, that the part sticking out of the heart wall should be as small as possible.

Because with our method of fixation the various curves obtained were free from artifacts, the zero line ran smoothly. The heart action continued undisturbed, even when 4-needle electrodes had been kept in the heart for several hours.

It was very important to know which electrode was in the cavity during the QRS complex. Since the innermost layers of the heart wall shift along the electrode lying in position, it cannot be deduced from the presence of an S-T deviation that the leadpoint was not in the cavity during the QRS complex. The criteria to which a given complex must conform, if one is to be able to assume that the leadpoint is lying in the cavity, can be found only in the QRS complex. These are as follows:

1. The complex in the cavity (Figs. 6 to 8) is more or less symmetrical, whereas the complexes in the inner layers of the heart wall show in the first part of the QRS complex a more or less marked fast portion, but otherwise differ little from the cavity curve. It is sometimes very difficult to decide whether a leadpoint is situated in the innermost layers of the heart wall. As a rule, however, with high amplification and a fast time basis, it was possible to reach a correct conclusion with the aid of this criterion.

2. The shape of the complexes registered between two leadpoints lying in the cavity is regular and does not show the relatively capricious course of the complexes registered between two leadpoints lying in the innermost layers.

The polarity of the complexes registered can give rise to confusion. Some curves are shown in which an upward deflection means negativity of the exploring electrode, for example, in some of the unipolar intramural complexes. This is always carefully indicated in the legend.

RESULTS

Intramural Unipolar Leads.—The intramural complexes show a few characteristics that are worthy of comment. Fig. 6 is a typical example. We see that the leadpoint 2 is situated in the ventricular cavity. The deep QS complex has a nearly symmetrical course. The course of complex 3 and 4 differs from that of the complex recorded in the ventricular cavity in that we observe a steep portion in the first part of the descending limb of the QS complex.

In the complex recorded at leadpoint 4, we observe a small elevation in the first part, preceding the deep negative deflection. This small positive deflection remains the same in all higher leads, even in the epicardial lead, where it is a small positive wave, preceding the R wave. In unipolar leads of other parts of the wall it was absent (Fig. 6).

In the unipolar lead of leadpoint 7, on the place in the complex where in the epicardial lead an R wave appears, an embryonic R wave, not reaching the base line, is seen. This deflection reaches the base line in the unipolar lead of 8 and crosses it in the epicardial lead. Thus predominantly negative complexes were registered at a distance of 8 to 10 mm. from the endocardium. The S wave of 6 is less deep than that of 5; the reduction of the voltages of this deflection is still more evident in 7 and 8. The voltage of the S wave in the epicardial lead is the least in all leads. It appears that the closer the intramural lead is to the epicardium, the smaller the voltage of all ventricular deflections.

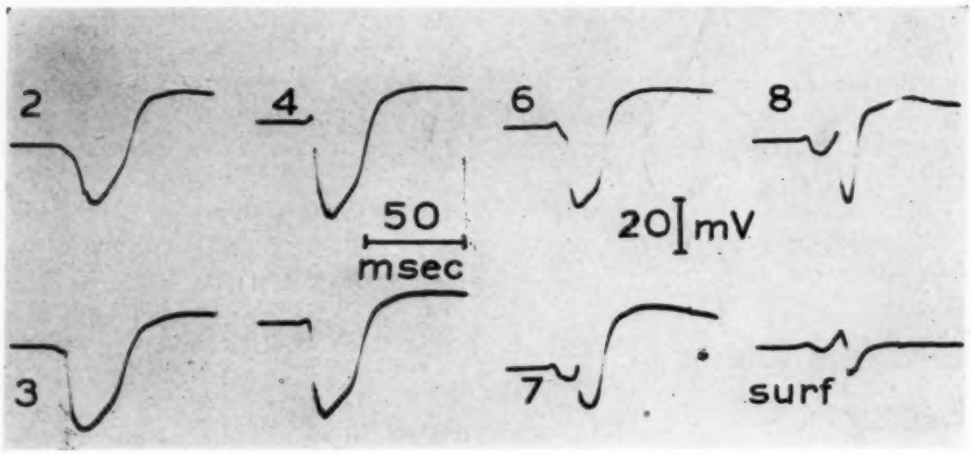

Fig. 6.—An 8-electrode needle was introduced into the heart wall. Leadpoint 2 is lying in the ventricular cavity; leadpoint 8 is closest to the epicardium.

The unipolar intramural complexes are predominantly negative. An embryonic R wave occurs in the unipolar lead. The surface complex has the smallest voltage. Note the rapid deflection in all unipolar intramural complexes. 2 is lying just at the endocardium, so here occurs no fast deflection. Note the S-T deviation.

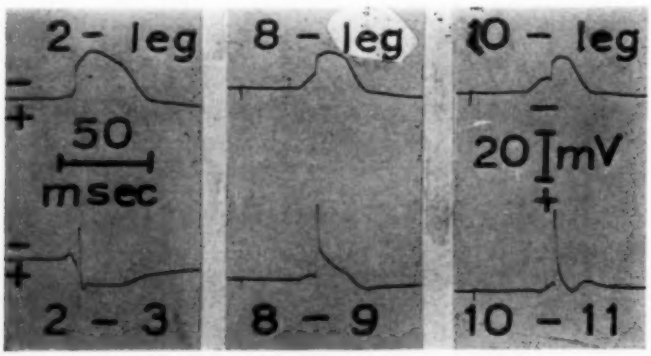

Fig. 7.—Note polarity of the unipolar complexes (upper row in all tracings). The lower complexes are from differential electrodes, placed in the heart wall. The upper curves are unipolar complexes, registered between one of the leadpoints of the differential electrode and the left leg. Note that the differential spikes occur synchronously with the rapid part in the intramural curve.

The behavior of the R wave is very interesting. Only in the outer layers of the ventricular wall do small R waves appear. In the greater part of the wall, deep negative complexes are seen. Prinzmetal and associates,[8] using single

intramural electrodes, found this surprising fact, too. They are of the opinion that ". . . this finding may be related to the penetration of the Purkinje system into the ventricular wall or to as yet undiscovered biochemical and/or enzymatic differences within the ventricular myocardium." We will try to give an analysis of these facts in a subsequent paper.

We saw a fast phase in all intramural curves. For the complexes recorded at leadpoints situated in the inner layers, the quick part fell in the beginning of the QS complex. For leadpoints placed in the outer layers it fell in the declining phase of the embryonal R waves.

The fast phase of these intramural curves appears when the muscle layer where the leadpoint is situated is activated. To demonstrate this a differential needle-electrode (Fig. 7) is placed in the wall of the heart. The potential variations of one of the leadpoints of this differential electrode were registered synchronously with the differential electrocardiogram. It appeared that the spikes in the differential electrocardiogram occur at the same time as the fast part of the intramural complex. This rapid deflection can be called the intrinsic deflection of the muscle layer in which the intramural leadpoint is situated.

These phenomena could be shown in all parts of the free wall of the left ventricle that were investigated. At long distances from the endocardium extending into the outer one-half of the wall, QS complexes are found. In the layers of the wall that are closer to the epicardium, R waves gradually appear in these QS complexes. In the zone where these complexes are found, the activation of the part of the wall situated between the intramural leadpoint and the endocardium causes only slight modifications of the pattern of the complexes found in the cavity.

Analysis of Unipolar Intramural Curves.—For the analysis of these unipolar intramural curves it is desirable to know the course of the cavity potential at the place under the part of the wall involved, in addition to the action curve produced by the activation of that part of the wall lying between the cavity and the intramural leadpoint. The last curve is the partial wall curve. The leadpoint placed closest to the epicardium was always connected with that part of the differential amplifier that gave a positive deflection with a positive potential. The partial wall curves of the inner layers are small and positive (Fig. 8). It is clear that the positive influence caused by activation of this part of the wall on the intramural leadpoint considered is negligible with respect to the great negativity of the cavity. Higher voltages are seen in the partial wall curve of greater portions of the wall. The intramural leadpoint is then situated in the outer layers. These higher voltages are responsible, therefore, for that part of the resulting unipolar intramural curve progressing to or above the base line (R wave).

If the partial wall curves of the consecutive leadpoints in the wall are compared, a very interesting phenomenon is seen. Frequently, the voltage of the partial wall curve of the inner layers increases in proportion to the thickness of the section of the wall being investigated, but the duration of the complex does not show an appreciable increase in time. In contrast, the height of the partial wall curves with the intramural leadpoint in the outer layers is constant, but the duration of the complex increases with the thickness of the part of the wall investigated.

The end of the positive deflection of the partial wall curve is always recorded at precisely the same time as the fast part of the intramural unipolar curves.

Time relation of the intrinsic deflections in the unipolar intramural curves: If we compare the time relations of the intrinsic deflections in the various unipolar intramural leads, it is evident that in the inner layers these parts appear within

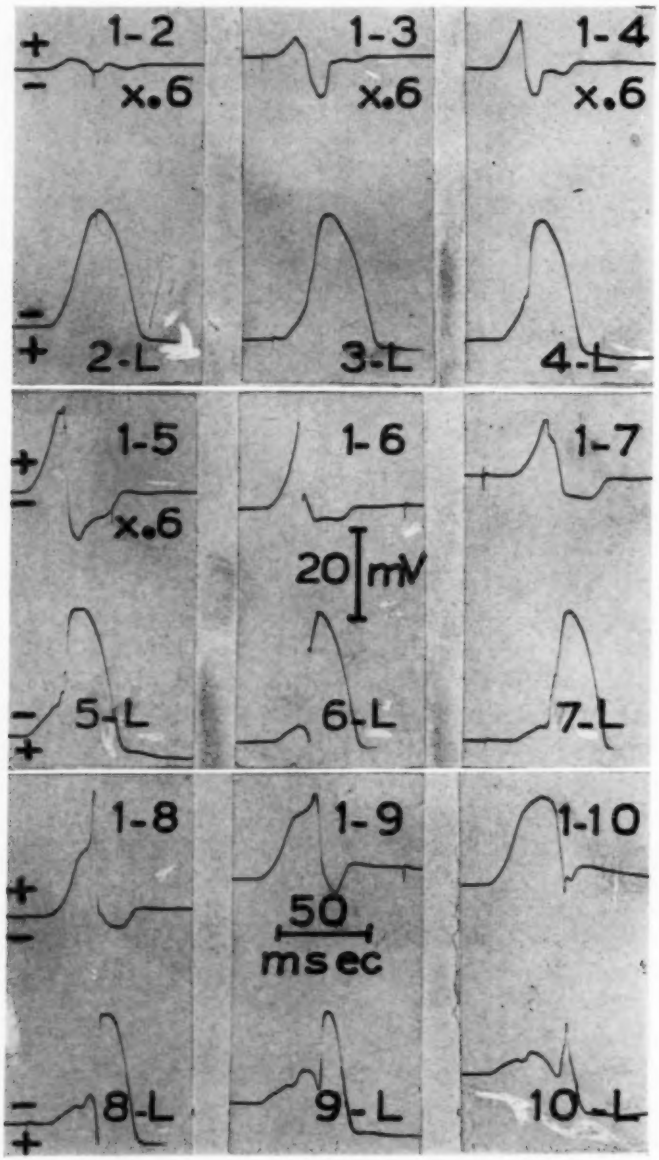

Fig. 8.—Note polarity of the unipolar intramural complexes. The partial wall curves of all intramural leadpoints were taken together with the unipolar leads of the corresponding intramural leadpoint. Leadpoint 2 is situated in the cavity. The sensitivity of the recording of the partial wall curves from leadpoints 2, 3, 4 and 5, was increased by 1.66 compared with that of 6, 7, etc. Note that the partial wall curves of the inner layers have approximately the same duration and that the voltage increases with the thickness of the muscle layer between electrode in cavity and intramural leadpoint. In the outer layers the voltage remains constant, but the duration of the complexes increases.

narrow time limits. It is only in the external layers that these intrinsic deflections appear consecutively.

It is not possible to investigate satisfactorily the spread of the activation wave in this manner. The spread of activation can be seen more clearly when the potential variations between the consecutive leadpoints are recorded. A positive deflection in the resulting curve points to positivity of the leadpoint placed closest to the epicardium.

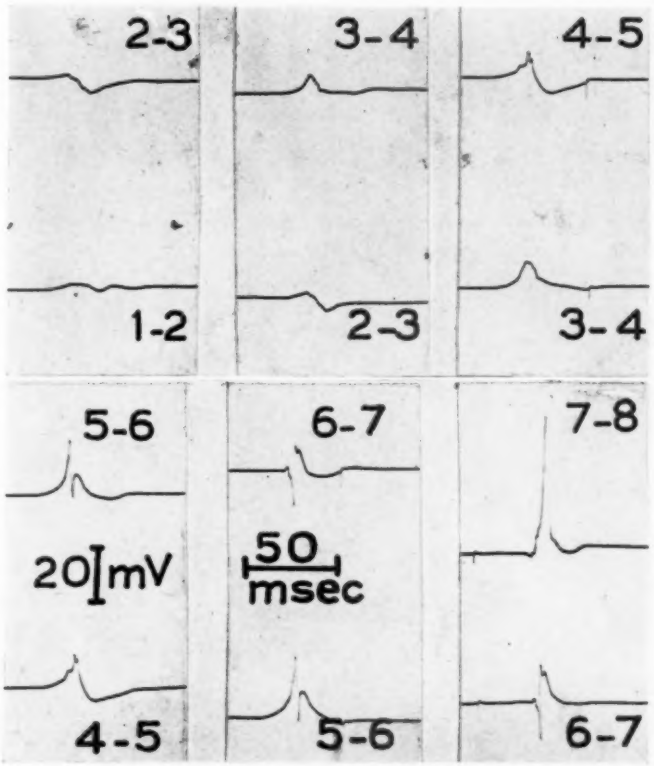

Fig. 9.—The potential variations between the intramural leadpoints are mutually registered. In this case the potential variations between a certain leadpoint and the next one are registered. In this manner it is possible to obtain information on the activation of the successive layers of the heart wall. In this experiment an 8-electrode needle was used. Leadpoint 3 is lying in the ventricular wall, close to the endocardium. 8 is the leadpoint nearest to the epicardium. Note the smallness of the complexes between 3 and 4, compared with those between 7 and 8. The last two leadpoints are lying in the regularly activated outer layers. Note the reversal phenomenon between 6 and 7.

Intramural Bipolar Leads.—

A. Inner layers: The complexes recorded between two consecutively placed leadpoints in the inner layers have the following characteristics (Fig. 9). They are often positive and small and usually show a slight irregularity in form, occasionally with deep notches. The time interval in which these complexes occur is small (4 to 6 milliseconds).

This is clearly seen when the potential variations between two points placed further apart are registered. It appears that the voltage and not the duration of complexes in the innermost layers increases with an increase in the distance

between the 2 leadpoints (Fig. 10). This layer is approximately one-third to one-half of the thickness of the wall. It is possible to explain this finding by assuming that these layers are activated more or less synchronously.

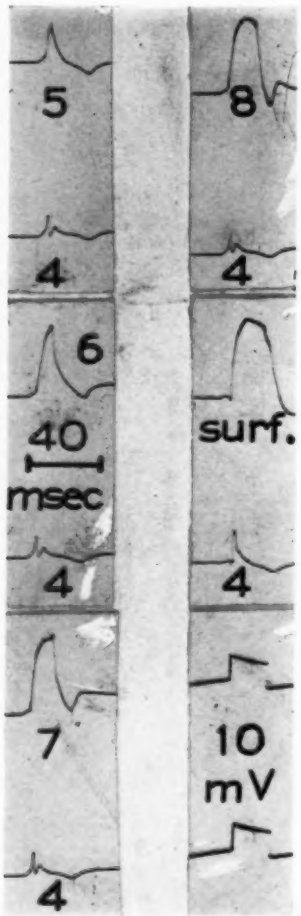

Fig. 10.—The lower complex in all rows is a lead between leadpoints 3 and 4, situated in the inner layers of the heart wall. In the other leads also, leadpoint 3 was constant; the number denounces the other leadpoint taken. Note that 3-5 is higher than 3-4, also the height of 3-6 increases, but the complex is somewhat broader too. 3-7, 3-8, and 3-surface have the same voltage; the width increases. 3-4 and 3-surface were taken 15 minutes later. The form of 3-4 has altered slightly.

B. Outer layers: The complexes between the consecutive leadpoints in the outer layers have a broad, high, positive maximum, often preceded or followed by a small negative deflection that occasionally may be absent. A fast portion is nearly always found in the ascending and descending limbs of these deflections. The width of the complexes increases proportionally to the distance between the intramural leadpoints. The voltage does not change. In Fig. 11 the complex between 9 and 11 is twice as wide as between 9 and 10. This shows that the maximum voltage caused by activation of a muscle layer can be measured when the activation process is between 2 leadpoints placed 2 mm. apart.

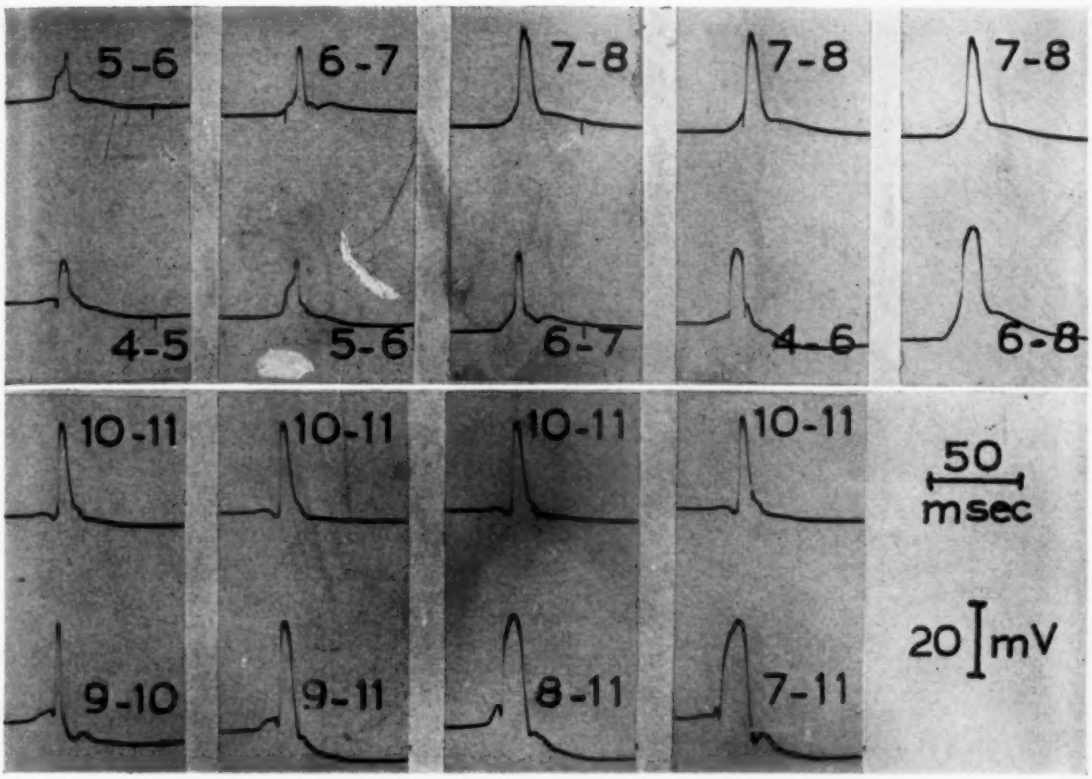

Fig. 11.—An 11-electrode needle with a distance of 2 mm. between the leadpoints was used. All leadpoints shown are lying in the successively activated wall layers.

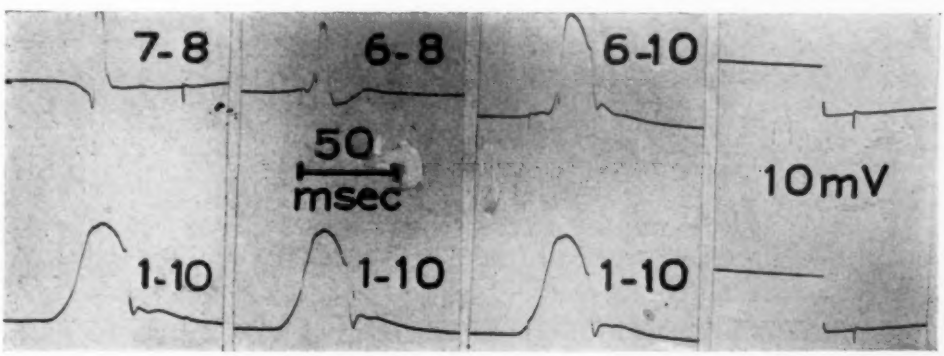

Fig. 12.—The lower complexes are between leadpoint 1 and 10. Leadpoint 10 was lying on the epicardial surface of the heart wall, leadpoint 6 was 8 mm. closer to the endocardium. Note that the complex between 6-10 has the same voltage as that between 1-10. The last parts of both curves are nearly identical.

The same phenomenon of the outer layers can be shown when a needle with leadpoints placed 1 mm. apart is used. The width of the complexes registered with this type of needle also increased proportionally with the distance between 2 leadpoints. This shows that the dipole front caused by activation of the outer layers of the heart has a distance, between sources and sinks, smaller than 1 mm. The steep part in the ascending and descending limbs of the action curves can be explained by assuming that the dipole front is sharply defined.

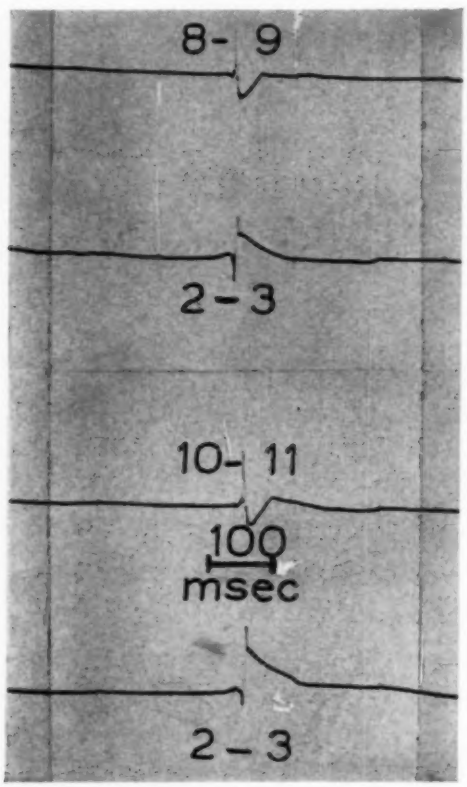

Fig. 13.—A 5-differential needle was introduced into the heart wall until all the differential leadpoints were lying in the inner layers. The differential spikes of all differential leads occur on the same moment. Leadpoint 1 was situated at the tip of the differential needle, leadpoints 2 and 3 are lying closest to the tip of the needle.

From Fig. 12 it follows that the precipitous descent that is seen at the end of the wall curves is caused by activation of the subepicardial muscle layer. Between the epicardial electrode and the leadpoint situated a few millimeters under the surface, an activation curve with the same fast part in the descending limb of the curve is always found. The height of the complexes from the external layers is the same as the voltage of the wall curve. The broad maximum of the wall complexes is caused by contribution of potentials from the successively activated parts of the heart wall.

Intramural Differential Leads.—The differences in activation of inner and outer layers can be shown in the following manner. A differential needle was introduced into the heart wall until all differential electrodes were situated in the inner layers. Fig. 13 shows that the spikes in the consecutive differential electrodes of a 5-differential-needle electrode occur nearly synchronously. When

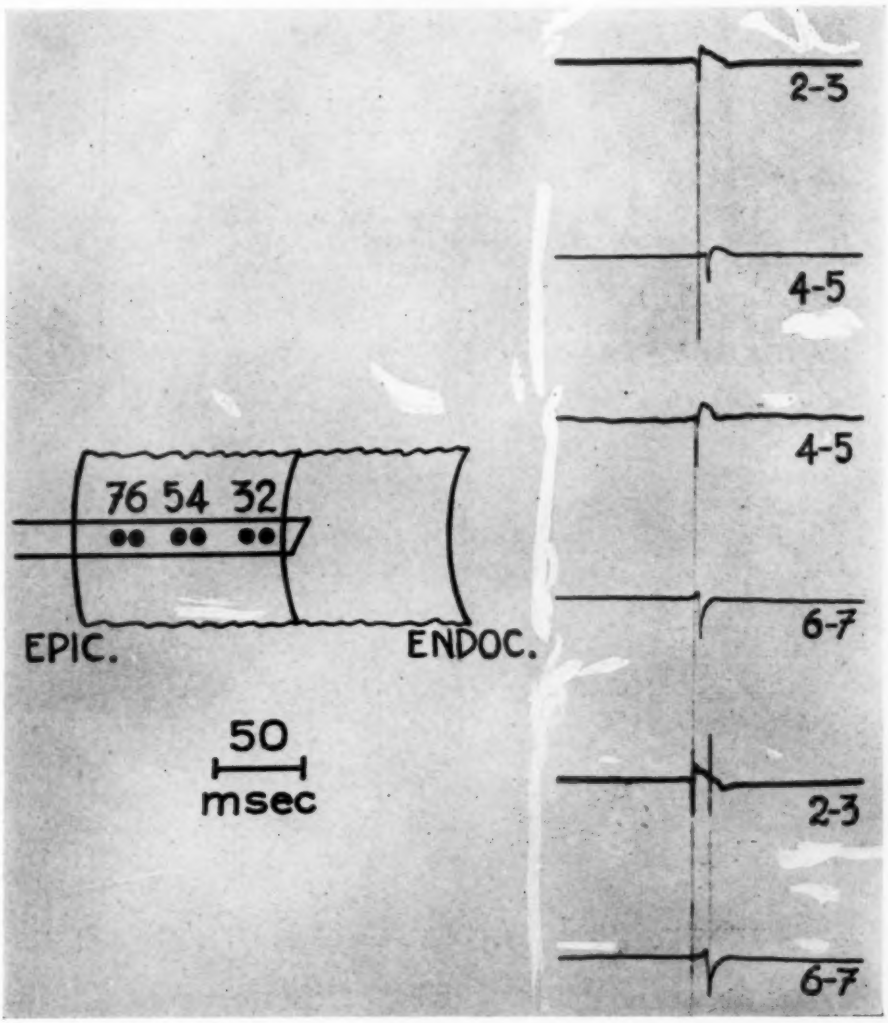

Fig. 14.—A 3-differential needle was drawn back until all differential electrodes were lying in the outer one-half of the heart wall. Now the differential spikes occur consecutively. The outer layers are activated consecutively.

a differential needle electrode was lying in the outer layers, the spikes of the consecutive differential electrodes now appear consecutively. This is illustrated for a 3-differential needle in Fig. 14. The speed of conduction measured in this manner is approximately 50 cm. per second.

Reversal Phenomenon.—A deep negative deflection at the beginning of the bipolar intramural complexes can be shown in some muscle layers of the ventricular wall (Fig. 9). In some cases the whole complex is almost entirely negative (Fig. 15, first complex between 3-4). It occurs nearly synchronously with the other deflections in bipolar leads in the inner layers. These layers can be found mostly in the transition zone between synchronously activated and successively

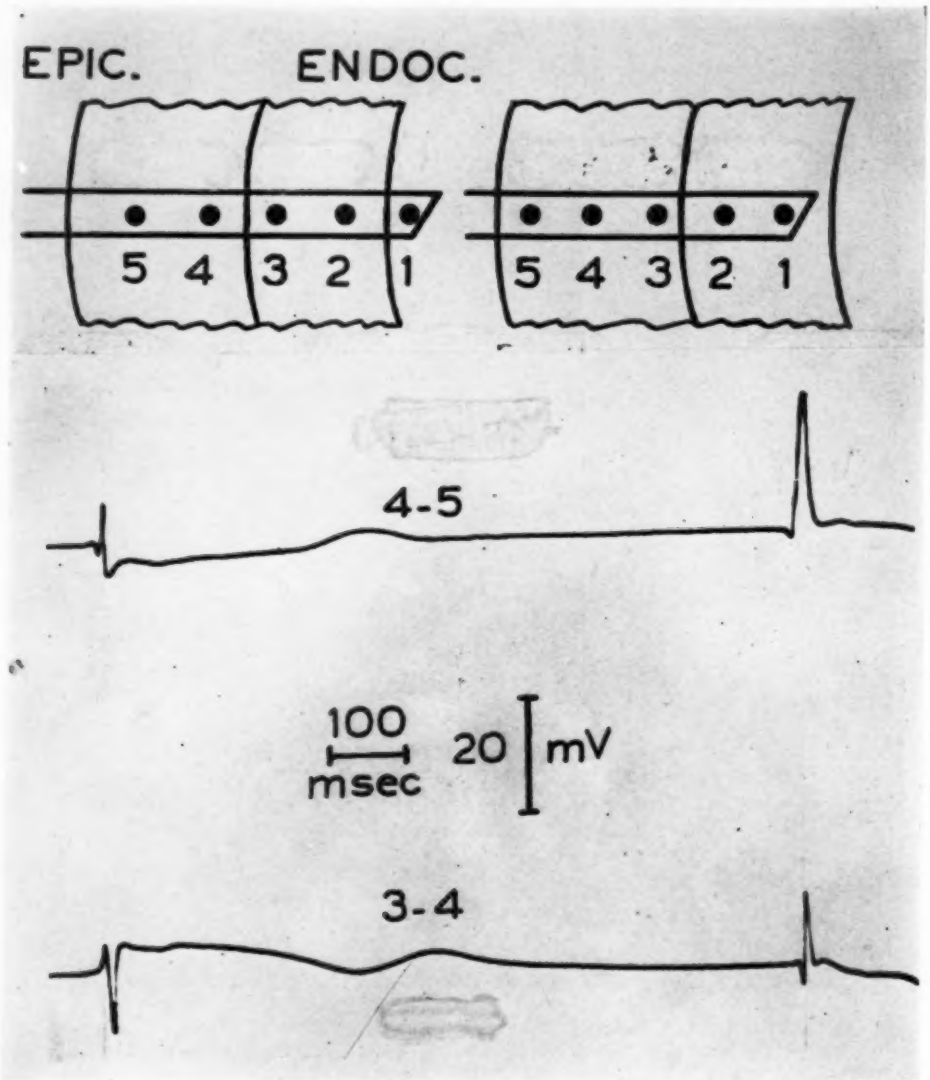

Fig. 15.—An 8-electrode needle was introduced into the heart wall. A reversal phenomenon was found. An upward deflection in these leads means positivity of the epicardially placed electrode. The negativity of the first complex in lead 3-4 is caused by activation of the muscle layer between 3 and 4, in a direction from epicardium to endocardium. The needle was withdrawn, until 3 and 4 were lying in the muscle layer, where before 4 and 5 were situated. Both complexes now have the same polarity, pointing to activation from endocardium to epicardium. The first complexes in both rows occur nearly synchronously; the second complexes come one after another.

activated parts of the wall. In the outer layers the maximum is preceded by a negative deflection, but a much smaller one, caused by the approach of the activation wave occurring in the adjacent underlying muscle layer. In the case of the deflection under consideration, however, the depth and the time relations make this explanation improbable. The most probable explanation is that the negativity is caused by activation of a greater part of the muscle layer between the leadpoints in an epi-endocardial direction.

The fact that these processes which cause the negative deflection are peculiar to a definite layer can be shown in the following manner (Fig. 15). After the introduction of the needle an area is sought that would give negative complexes between two adjacent electrodes. While continuous recordings are made, the needle is withdrawn a distance equal to the distance between two leadpoints. The leadpoints which show a reversal phenomenon between them are now situated in a layer activated regularly. The reversal phenomenon disappears and is replaced by a complex that shows activation in an endo-epicardial direction.

The following hypothesis for this reversal phenomenon can be offered. The inner layers of the left ventricular wall are penetrated to a depth of approximately one-third of the thickness of the wall by rapidly conducting fibers, i.e., Purkinje fibers. The network is dense in the layers close to the endocardium but becomes looser in epicardial direction. It is absent in the successively activated outer layers, which are activated by muscle conduction. A Purkinje fiber in the transitional zone between these differently activated layers gives rise to an activation wave in the normal direction but finds excitable muscle fibers in endocardial direction too. It depends on the dimensions of the Purkinje network whether an activation wave in this direction can occur. If the meshes are wide, the terminations of the Purkinje fibers in the transition zone are surrounded by relatively large numbers of muscle fibers without Purkinje cells, which are activated by muscle transmission. It is tempting to assume a termination of the Purkinje system in the transition zone, with again a greater density of fibers, to account for the comparatively high voltages sometimes shown by the reversed complexes.

The influence of extrasystoles caused by stimulation of endocardially or epicardially situated muscle layers on the reversal phenomenon will be reported on at a later date, but the results are compatible with the explanation offered above.

The results of Prinzmetal and associates[8,10] and Scher and associates[9,11] will also be discussed in a later publication.

SUMMARY

Important information as to the course of activation in the heart wall can be obtained from the transmural wall curve. This is but little influenced by the other parts of the heart, a fact that can be demonstrated by studying the influence of septum activation on it. The wall curve is highly asymmetric, and its fall has a very steep part. This fast portion is synchronous with the fast part of the corresponding unipolar epicardial lead. The P-R interval of the epicardial lead differs from that of the transmural lead: the former is 10 to 15

milliseconds longer than the latter. This is explained by the course of the cavity potential and the wall curve. The descending part of the cavity curve and the ascending part of the wall curve are nearly identical. The causes of this remarkable phenomenon are analyzed.

The cavity potential comprises potential contributions from the wall activation and septum activation. The transmural potential originates nearly totally from activation of the free wall. Since the electrodes lie on either side of the activation front, the transmural potential is higher than that part of the cavity potential that originates from the wall activation. The contribution of the septum activation to the cavity potential makes the latter more or less equal to the transmural potential.

In view of the fact that even the wall curve can give only a rough picture of the activation of the wall, the latter has been examined by means of needle electrodes. It was shown that despite the movements of the heart it is possible to fix the electrodes satisfactorily. The lesion effects following insertion of the needle disappear within 15 minutes at the most. The surrounding tissue remains sufficiently intact.

Unipolar intramural leads and partial wall curves were registered synchronously. The latter were registered between an intramural leadpoint and a cavity electrode, placed close to the endocardium of the wall area in question.

The unipolar intramural curves were strongly negative in a large part of the wall; R-waves occurred only in the outermost layers. The complex at the epicardial surface is the smallest of the series. The partial wall curves of the innermost layers show, in correspondence to this, a low voltage. Only in the outer layers does the shape of the partial wall curve approach that of the wall curve for the region in question.

Both the unipolar intramural and the partial wall curves show larger or smaller fast portions; these are due to the activation of the layer in which the leadpoint in question is situated.

A more accurate analysis can be achieved by taking bipolar leads from the closely-spaced leadpoints of an electrode needle and by the use of a differential needle electrode. In this way it has been shown that the innermost layers are more or less synchronously activated. In consequence of this the activation front in these layers is irregular in shape and the voltage does not reach the same values as in the outermost layers. In the bipolar leads this is shown by the small, irregular complexes.

The activation of the outer layers, on the other hand, gives rise to regularly formed complexes, the width of which is proportional to the distance between the leadpoints. This indicates that the front is regular in form and sharply bounded. The velocity of propagation in these layers is approximately 50 cm./sec.

Between the synchronously activated inner layers, which account for approximately two-fifths of the thickness of the wall and the outer layers there is in some areas a transitional region in which complexes, often regular in shape, are found which are indicative of activation in epi-endocardial direction.

A hypothesis accounting for these facts is presented.

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STUDIES OF THE P LOOP OF THE SPATIAL VECTORCARDIOGRAM: THE NORMAL P LOOP

NOBLE O. FOWLER, M.D., AND EDWARD R. DORNEY, M.D.

BROOKLYN, N. Y.

IN published studies of the human spatial vectorcardiogram, there have been few references to the loop formed by electrical activation of the atria. At standardizations employed for routine vectorcardiography, the normal P loop is seen with difficulty, if at all.[1] Since it is known that patients with rheumatic mitral stenosis may have normal electrocardiograms, including the P wave, it seemed desirable to ascertain whether or not abnormalities of the P loop of the spatial vectorcardiogram might be present in such patients. As a preliminary to such study, it became necessary to establish a normal pattern for the P loop as recorded by the cube reference system.[2] This paper describes the results of this study.

MATERIAL

The normal subjects studied were thirty-one house officers and student nurses from the staff of the Brooklyn Hospital. Their ages ranged from 17 to 34 years. None had evidence of heart disease by history, physical examination, and twelve-lead scalar electrocardiograms.

METHOD

Spatial vectorcardiograms were recorded by the cube reference system of Grishman and associates,[2] using equal standardization for the horizontal, vertical, and anteroposterior components. The frontal projection of the spatial loops was viewed from the front of the erect subject; the sagittal projection was viewed from the right side of the erect subject. The transverse projection was viewed as if looking toward the prone subject in a head-to-foot direction. The vectorcardiograms were recorded at a low sensitivity of 5.5 to 10 cm./mv. for study of the QRS loops, and then, for study of the P loops, at a sensitivity of 30 to 45 cm./mv. Frontal, sagittal, and transverse projections of the spatial loops were recorded in rapid succession rather than simultaneously. The loops were photographed from the face of a seven inch R.C.A. WO-56A cathode-ray oscilloscope upon 35 mm. film and enlarged by projection for study. Interruption of the cathode-ray beam at intervals of 0.004 sec. with tapering of the segments in the direction of inscription was produced by means of a modified square-wave generator.

From the Cardiac Laboratory, Brooklyn Hospital, and the Department of Medicine, State University of New York, New York, N. Y.

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RESULTS

All subjects had normal QRS and T loops in the three plane projections of the spatial loops. Of the thirty-one subjects, twenty-six had P loops which could be used for measurement. In the others, electrical hum interfered with proper visualization of the P loops. All P loops appeared to return to the isoelectric point at the end of inscription. In some instances there was a small gap at the isoelectric point. This was too small or inconstant to be certain that the P loop failed to close. The P loop, because of its elongated shape and nearly vertical direction, could not be studied satisfactorily in the transverse plane in any of these normal subjects. The amplitude of the P loop could be measured in twenty-four subjects in the frontal plane and in twenty-six subjects in the sagittal plane. The direction of inscription of the P loop could be seen in the photographs in twenty-three subjects in the frontal plane, and in only eighteen in the sagittal plane. In the sagittal plane, the P loop was often nearly linear and irregular in its course.

Amplitude.—As may be seen in Table I, the amplitude of the P loop in the frontal plane ranged from 0.08 to 0.21 mv. with a mean of 0.131 mv. In the sagittal plane, the amplitude ranged from 0.06 to 0.28 millivolt, with a mean of 0.128.

TABLE I. NORMAL P LOOPS OF THE SPATIAL VECTORCARDIOGRAM

	DIRECTION OF INSCRIPTION			
	CLOCKWISE	COUNTERCLOCKWISE	FIGURE -8	LINE
Frontal	0	21	1	1
Sagittal	8	0	8	2

	AMPLITUDE IN MILLIVOLTS		STANDARD DEVIATION
	RANGE LIMITS	MEAN	
Frontal	0.08 to 0.21	0.131	0.038
Sagittal	0.06 to 0.28	0.128	0.056

	ANGLES IN DEGREES*		STANDARD DEVIATION
	RANGE LIMITS	MEAN	
Frontal	60 to 93	78.8	10.6
Sagittal	70 to 100	84	5.7

*Angles are measured in a clockwise direction from the observer's right end of the x axis in the frontal plane and from the observer's right end of the z axis in the sagittal plane.

Direction of Inscription.—In the frontal plane, the direction of inscription was, in general, counterclockwise. Twenty-one of twenty-three subjects demonstrated a counterclockwise P loop in the frontal plane; in one, the loop was

linear; in one, the configuration was that of a figure 8. In the sagittal plane, eight loops were inscribed clockwise; eight were figure 8's, and two were linear. Representative P loops are pictured in Figs. 1 and 2. Fig. 1 shows in the upper row the normal frontal, sagittal, and transverse projections of the spatial QRS-T loops recorded from one individual at a gain of 5.5 cm./mv. The P loops are not discernible at this amplitude. In the lower row of Fig. 1 are shown frontal and sagittal projections of the P loop of this subject at a gain of 42.5 cm./ mv. The P loop is inscribed in a clockwise direction in the sagittal plane and in a counterclockwise direction in the frontal plane.

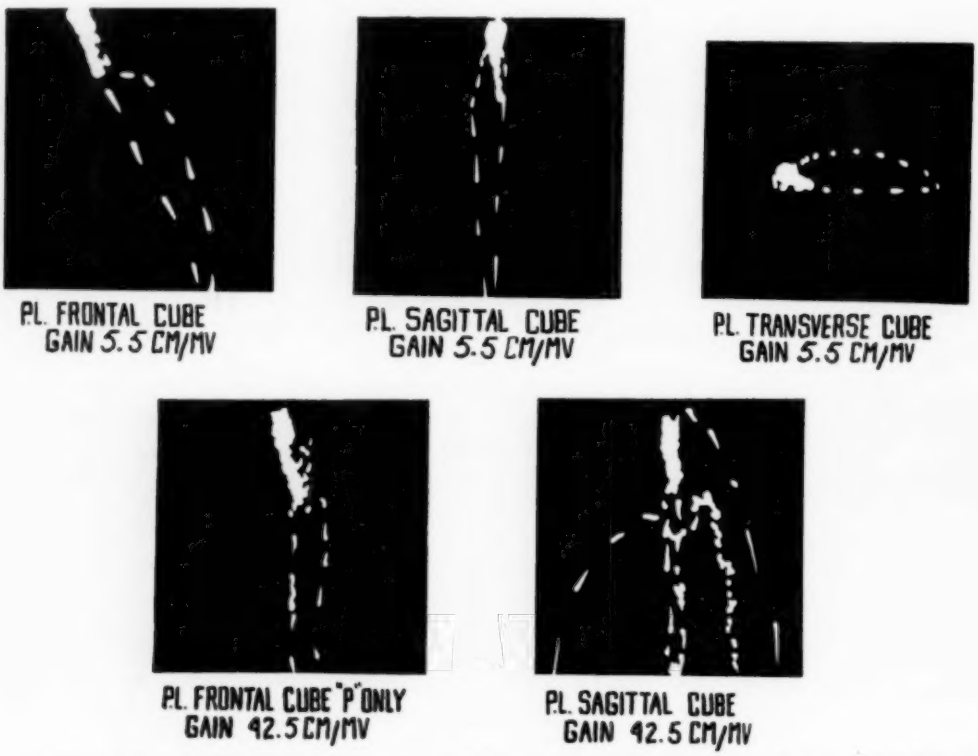

Fig. 1.—Normal spatial vectorcardiograms recorded by the cube system. Interruptions are at intervals of 0.004 sec., and are tapered in the direction of inscription. In the upper row, loops are shown at a gain of 5.5. cm./mv. In the lower row, loops are shown at a gain of 42.5 cm./mv. In the upper left corner, is shown the frontal plane QRS loop, inscribed in a counterclockwise direction. In the upper center is shown the sagittal projection of the same loop, inscribed in a clockwise direction. In the upper right is seen the transverse (horizontal) projection of the QRS loop, which is inscribed in a counterclockwise direction. In the upper row, P loops are not visualized, and T loops are seen as solid white ovals extending from the isoelectric point in a direction roughly parallel to the QRS loop. In the lower left photograph is shown a frontal projection of the isolated P loop of the same subject, inscribed in a counterclockwise direction. At the lower right is shown the sagittal projection of the P loop, whose long axis is vertical, and whose direction of inscription is clockwise. A portion of the T loop is seen anterior to the P loop, and surrounding both is a portion of the QRS loop, which is inscribed in a clockwise direction.

Fig. 2 demonstrates in the upper row QRS-T loops at a gain of 7.5 cm./mv. The P loops are not seen. In the lower row at the left are shown the P and T loops at a gain of 42.5 cm./mv. without timing interruption. The P is the more vertical of the two loops. In the center of the lower row is shown a projection at

the same gain with timing interruption. It may be seen that the frontal plane P loop is inscribed in a counterclockwise direction. In the lower right photograph of Fig. 2 is shown a large vertical P loop in sagittal projection, inscribed as a figure 8.

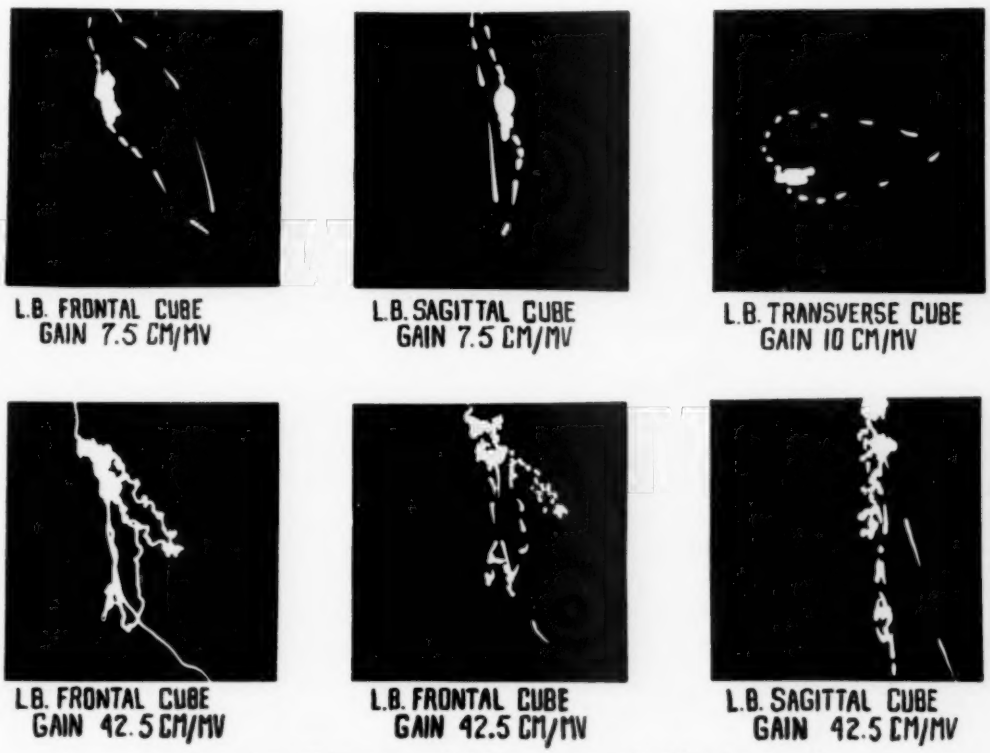

Fig. 2.—Spatial vectorcardiograms recorded from one normal subject by the cube system. The interruptions are the same as in Fig. 1. In the upper row are shown from left-to-right the frontal, sagittal, and transverse projections of the spatial loops, recorded at a gain of 7.5 cm./mv. The P loops are not seen in the upper row, and the T loops again appear as short solid white ovals extending from the isoelectric point roughly parallel to the QRS loop. In the lower row are shown the same loops recorded at a gain of 42.5 cm./mv. At the lower left is the frontal projection recorded without interruption, showing the more vertical P loop and the T loop above and to the left. Only a small portion of the QRS loop is seen. In the lower center, the same view with interruption shows that the P loop is inscribed in a counterclockwise direction. At the lower right, a portion of the QRS loop is seen in sagittal projection, inscribed in a clockwise direction. The long vertical figure-8 P loop is seen along the posterior limb of the QRS loop, and the T loop is smaller, superior, and posterior to the P loop. The apparent failure of the P loop to close completely is due to slight shifting of the isoelectric point during photography.

Angle of the Long Axis of the P Loop.—Although integration was not used to determine the direction of the mean P vector, the loops were so nearly linear that but slight error was involved in using instead the direction of the largest P vector for angular measurements. In the frontal plane, angles were measured in a clockwise direction from the observer's right end of the x (horizontal) axis to the largest P vector. In the sagittal plane, angles were measured in a clockwise direction from the observer's right end of the z axis (anteroposterior) to the largest P vector. The results are shown in Table I. In the frontal plane, angles

ranged from 60 to 93 degrees, with a mean of 78.8 degrees. In the sagittal plane, angles ranged from 70 to 100 degrees, with a mean of 84 degrees. Thus it may be seen that the average P loop is directed almost vertically from the isoelectric point, inclining to the left and slightly forward.

DISCUSSION

Few descriptions of the normal P loop of the spatial vectorcardiogram have been made. Because of its small size and position roughly parallel to the QRS and T loops, study of the normal P loop requires either great amplification, as employed in this study, or electrical "dissection" of the QRS and T loops to prevent their interference with the observation of the P loop.

In an abstract, Sano and co-workers[3] described the P loop in twelve normal subjects studied by the technique of electrical "dissection." In their cases, the P loops were usually inscribed in a counterclockwise direction in the frontal plane and in a clockwise direction in the sagittal plane. The reference system used was not given. Conway and associates[4] described P loops obtained by the equilateral tetrahedron reference system in sixteen normal subjects. Their direction was usually counterclockwise in both frontal and sagittal planes. Their loops were nearly vertical in the sagittal plane, as were ours; the direction of their frontal plane loops averaged 65 degrees as compared to 78.8 degrees in our subjects. The amplitude of the P loop in their study averaged twice that observed in ours. It is likely that the results are not entirely comparable because of the different systems used as reference.

All reference systems for spatial vectorcardiography in current use suffer from common difficulties because of the eccentric position of the heart in the chest and the lack of homogeneity in conducting properties of the body tissues. For this reason the chief value of the present study is to establish a base line for comparison with future studies in patients with heart disease. Preliminary studies have indicated that in some patients with mitral stenosis or cor pulmonale the P loops are larger in area and more irregular in contour than the normal. In addition in some instances the P loops fail to return to the isoelectric point following their inscription. These studies will be described in detail in a later paper.

SUMMARY AND CONCLUSIONS

1. Studies of the P loop of the spatial vectorcardiogram were made in twenty-six normal subjects, using the cube reference system.

2. In the frontal plane, the P loops were usually inscribed in a counterclockwise direction. In the sagittal plane, the direction of inscription was usually clockwise or figure 8.

3. The mean direction of the P loop in the frontal plane was 78.8 degrees from the x axis; in the sagittal plane, the mean direction was 84 degrees from the z axis.

4. The mean amplitude of the P loop was 0.131 mv. in the frontal plane and 0.128 mv. in the sagittal plane.

5. In the normal subjects, all P loops returned to the isoelectric point following inscription.

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PHEOCHROMOCYTOMA AND THE ABNORMAL ELECTROCARDIOGRAM

WILLIAM J. SAYER, CAPTAIN, MC, USA,* MARVIN MOSER, M.D.,** AND THOMAS W. MATTINGLY, COLONEL, MC, USA*

WASHINGTON, D. C.

PHEOCHROMOCYTOMA with surgical cure is no longer a medical rarity.[1] Nevertheless, since this tumor is still occasionally diagnosed only on the autopsy table,[2] there remains a constant need for appropriate clinical suspicion based upon a sound familiarity with all the characteristics of this disease.

The clinical features, the laboratory and metabolic abnormalities, and the medical and surgical management of patients with a pheochromocytoma have been extensively discussed.[3-7] Several chemodiagnostic tests have been devised and the utility as well as the pitfalls of these procedures have been adequately reviewed.[3,6,8-12a,b] There has been, however, no recent emphasis of the fact that electrocardiographic abnormalities are frequently noted in the presence of a functioning chromaffin cell tumor.

In order to direct attention to this feature of the clinical syndrome, the electrocardiographic changes encountered in two patients with surgically cured pheochromocytoma are presented, the pertinent literature reviewed, and the pathologic physiology of these abnormalities discussed.

CASE REPORTS

CASE 1.—A 29-year-old white woman was seen by a physician during the twenty-eighth week of her first pregnancy for treatment of "sinus headaches." Histamine base, 0.05 mg., administered subcutaneously, caused an immediate flush without reproduction of her typical headache. Thirty minutes later, generalized pallor and marked nervousness were observed. The administration of bacterial vaccine resulted in the disappearance of the headaches, and she remained asymptomatic with normal blood pressure and urinalyses until the thirty-sixth week of her pregnancy.

At this time she noted the onset of paroxysmal "attacks" consisting of marked tremor of the extremities followed immediately by palpitation in the epigastric, precordial, and substernal areas. A severe, generalized throbbing headache immediately ensued, followed by extreme apprehension, marked coolness of all extremities and occasional parasthesias. The duration of an "attack" was never more than one or two minutes, but the frequency of occurrence increased as her pregnancy progressed.

In March, 1951, using saddle-block anesthesia, she was delivered of a full-term normal infant. Immediately postpartum, a state of severe shock with pulmonary edema intervened.

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*Cardiology Section, Medical Service, Walter Reed Army Hospital, Washington, D. C.

**Present address: Thornycrofts Apts., Scarsdale, New York: Formerly Officer in Charge, Vascular Clinic, Walter Reed Army Hospital, Washington, D. C.

This did not respond to plasma, whole blood, oxygen, or ephedrine sulfate. There was no evidence of hemorrhage. After 12 hours of vasomotor collapse, she responded spontaneously with all vital signs becoming normal. At the time of her discharge from this hospital, the physical examination, chest x-ray, complete blood count, and urinalysis were normal.

One week later the "attacks" recurred with increasing frequency and severity. Three weeks postpartum her blood pressure, recorded during an attack, was 160/110 mm. Hg in contrast to her usual blood pressure of 110/70 mm. Hg and she was rehospitalized. A histamine test was positive and the patient was transferred to Walter Reed Army Hospital with the presumptive diagnosis of pheochromocytoma.

Physical examination: On May 1, 1951, an examination revealed a well-developed, poorly nourished white woman of stable disposition with a blood pressure reading of 100/64 mm. Hg and no abnormal physical findings. Attacks could not be produced by change of position or abdominal palpation; postural tachycardia and hypotension were not demonstrable and there were no abdominal masses or bruits.

Laboratory data: Repeated complete blood counts, urinalyses, serologic tests for syphilis, complete serum electrolyte determinations, blood urea nitrogen, serum proteins, and 24-hour urinary excretion of 17 ketosteroids were all within normal limits. Repeated basal metabolic rates were consistently low-normal. The glucose tolerance curve was abnormally high, and persistent fasting hyperglycemia without glycosuria was confirmed.

The chest x-ray was within normal limits, but excretory and retrograde urograms and abdominal laminography revealed lateral displacement and nonvisualization of the upper pole of the left kidney.

Hospital course: Preoperatively, blood pressure determinations varied between 80/40 to 240/110 mm. Hg, and a cold pressor test produced a rise of from 110/74 to 150/110 mm. Hg. For 36 hours after an exceptionally severe series of "attacks," postural hypotension and tachycardia were demonstrable. The day before surgery a left abdominal mass was palpable, and a bruit was heard in this area.

Exploratory laparotomy, utilizing a transverse epigastric incision, revealed a cystic tumor in the left adrenal area. Manipulation of the tumor resulted in a precipitous rise in blood pressure which was reduced by 1.5 mg. of intravenous Regitine. Shortly thereafter, the tumor ruptured into the peritoneal cavity and the blood pressure fell to shock levels. Constant intravenous administration of norepinephrine, 4 mg. per 1,000 c.c. of normal saline, was necessary until 36 hours after surgery for the maintenance of normal blood pressure. During this period the patient also received whole adrenal cortical extract, parenteral fluids, whole blood transfusions, and antibiotics. The convalescent period was uneventful and re-examination one year later which included a repeat histamine test, revealed the patient to be completely well.

Electrocardiographic description: The first electrocardiogram was taken after the episode of postpartum shock and revealed only sinus tachycardia and generalized low voltage. A tracing obtained following an exceptionally severe series of "attacks" recorded a wandering pacemaker within the sinoatrial node, Q-T interval of 0.44 sec. with rate of 98 per minute and inverted T waves in Leads I, II, aV_L, aV_F, and V_3 through V_6. Diphasic T waves were noted in Leads III and V_2 (Fig. 1,A). These changes persisted becoming somewhat less marked during the preoperative period.

At operation, during manipulation of the tumor, an intermittent wandering pacemaker between the atrioventricular and sinoauricular nodes and occasional nodal premature contractions were noted on the cardioscope.

The next significant change occurred postoperatively during norepinephrine infusion (Fig. 1,B) when high-peaked P waves, right-axis deviation, and upright configuration of some of the previously inverted T waves occurred. Immediately following cessation of the norepinephrine infusion, the electrocardiogram resumed the preoperative configuration (Fig. 1,A).

Two weeks after removal of the tumor (Fig. 1,C) the T waves were isoelectric in Lead I, inverted in aV_L, V_4 through V_6 and of low amplitude in Leads II and aV_F. Gradual reversion to a normal electrocardiogram (Fig. 1,D) was observed within six weeks of the operation.

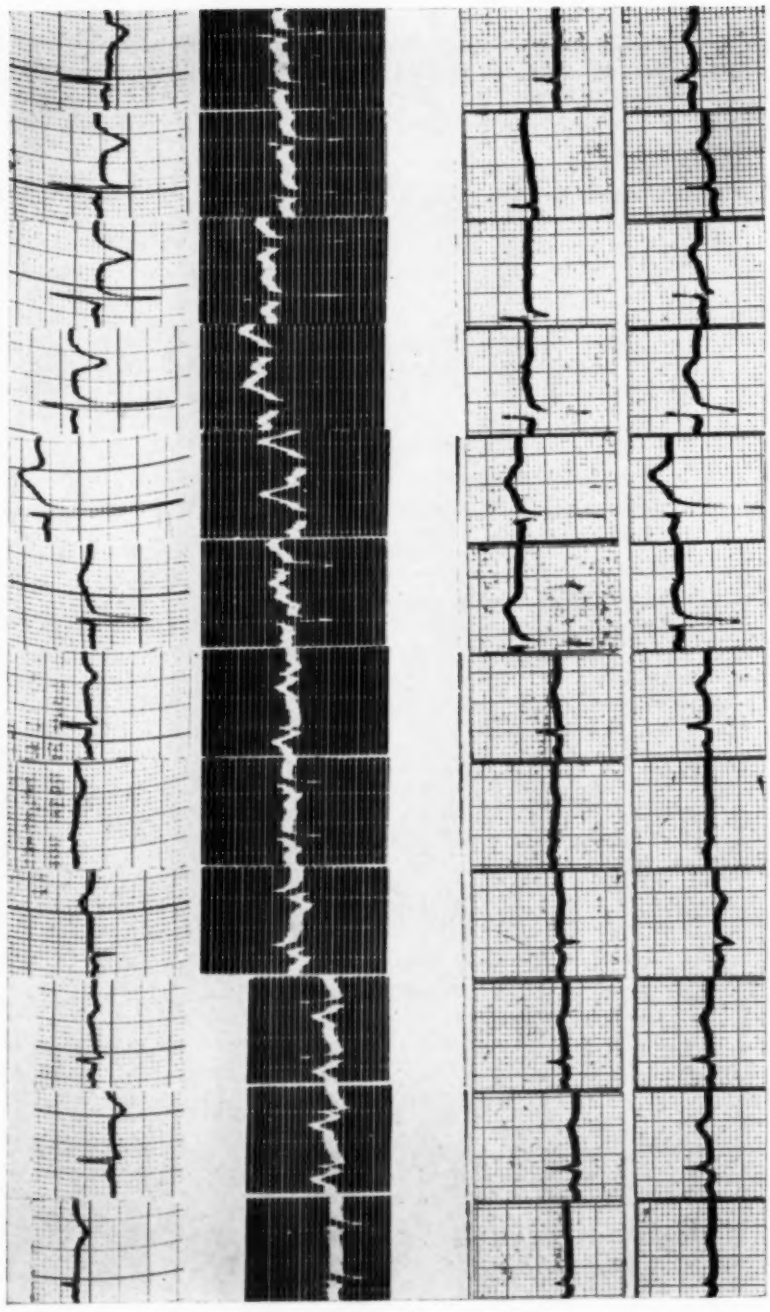

Fig. 1.—Case 1. Serial electrocardiograms illustrating pre- and postoperative findings and changes which occurred during norepinephrine infusion. *A*, Preoperative tracing, following severe series of paroxysms. *B*, During norepinephrine infusion. *C*, Postoperative two weeks. *D*, Six weeks postoperative.

CASE 2.—A 30-year-old white woman was in excellent health until the eighth month of her first pregnancy five years prior to the present admission. At that time she developed hypertension, ankle edema, and 3-plus albuminuria which disappeared after delivery. During another pregnancy, one year later, identical findings recurred and again disappeared after delivery. Two years prior to the present admission, during her third pregnancy, hypertension was again noted. This was accompanied by severe occipital headaches and episodes of "tenseness and profuse sweating" related to emotional stress. Following an uneventful delivery a sustained hypertension was recorded varying between 180/120 and 220/140 mm. Hg with a transient fall to a base line blood pressure of 120/90 when she was treated with bed rest and sedation. During the six months preceding the present admission, the hypertension and symptoms described above persisted with concomitant severe "impatience," occasional nocturia, and one brief episode of precordial pain.

Thorough studies at several hospitals revealed minimal electrocardiographic evidence of left ventricular hypertrophy, and Grade 2 retinopathy, with no other evidence of disease except the elevated blood pressure. She was transferred to Walter Reed Army Hospital for observation and treatment.

Physical examination: Abnormal physical findings on admission were limited to blood pressure of 180/120 mm. Hg, excessive perspiration, papilledema, retinal hemorrhages, and exudates.

Laboratory data: Complete blood count, serologic test for syphilis, phenolsulfonphthalein excretion, and Fishberg concentration test were all within normal limits. Repeated urinalyses revealed only an occasional trace of glycosuria and persistent 1-plus albuminuria. A fasting hyperglycemia and an abnormally high glucose tolerance curve were noted. Repeated basal metabolic rates were moderately elevated and the total eosinophil count was 25.

Chest x-ray and cardiac fluoroscopy suggested minimal left ventricular hypertrophy, and retrograde pyelography showed minimal downward and lateral displacement of the left kidney.

Hospital course: With bed rest the patient was asymptomatic except for excessive perspiration and blood pressure determinations which varied between 170/115 mm. Hg and 200/130. Following the intravenous injection of 40 mg. of hexamethonium, the patient's blood pressure in the sitting position fell from 180/130 mm. Hg to 90/60. On resuming the reclining position a rise to 270/160 mm. Hg occurred.* Since this reaction so closely paralleled that of patients with pheochromocytoma who are given intravenous tetraethyl ammonium chloride, the following tests were performed: (a) benzodioxane, 15 mg., intravenously, resulted in a fall of blood pressure within 5 minutes to 100/70 mm. Hg from a resting level of 200/130; (b) a blood pressure fall to 90/70 mm. Hg from 200/130 followed the intravenous injection of 30 mg. of Dibenzyline; (c) eighteen hours after this injection, when it was felt that the patient was still under partial adrenergic blockade, 0.025 mg. of histamine base was administered intravenously resulting in a rise of the blood pressure from 150/100 mm. Hg to 210/130; (d) oral Regitine, 60 mg. resulted in a lowering of the blood pressure to 100/70 mm. Hg from 200/124 within one hour of administration. These observations will be reported in detail elsewhere.[12b]

With the provisional diagnosis of pheochromocytoma of the left adrenal area, the patient was given oral Dibenzyline, 10 mg. three times daily, for one week until 24 hours prior to surgery with resultant maintenance of base line blood pressure determinations at 140/90 mm. Hg to 150/100.

At operation a pheochromocytoma of the left adrenal area was removed, and an immediate blood pressure fall ensued. This necessitated the constant intravenous administration of norepinephrine for a period of 7 hours after completion of surgery. The postoperative course was uneventful. Blood pressure levels were stabilized at 120/80 mm. Hg to 130/85; fundoscopic abnormalities cleared gradually; and blood sugar levels, eosinophil count, and the basal metabolic rate all returned to normal levels. Following a negative histamine test the patient was discharged and has remained asymptomatic for ten months following surgery.

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*Since hexamethonium is now being widely used in the study and therapy of essential hypertension, this unusual response should be looked for as a possible indication of a pheochromocytoma.

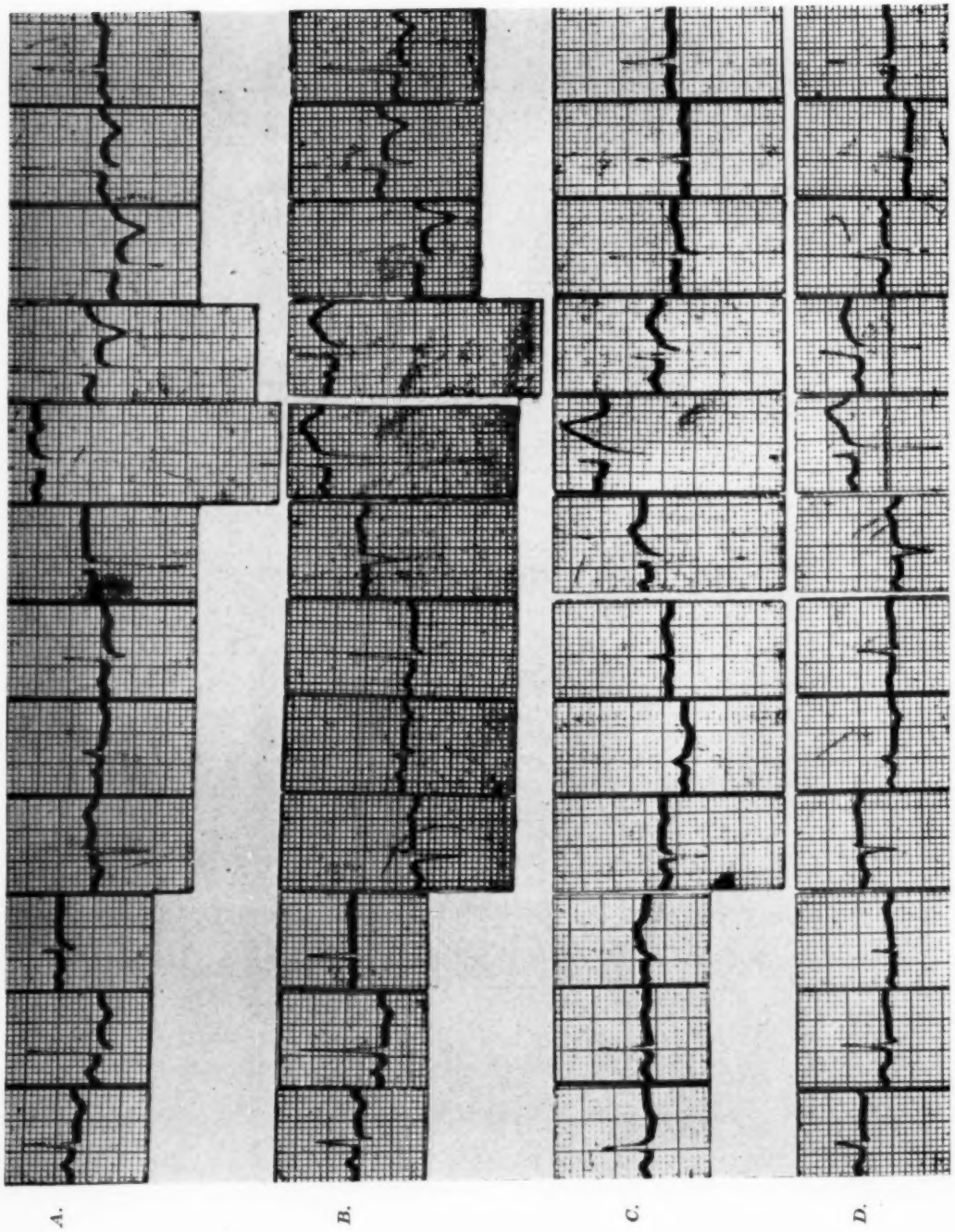

Fig. 2.—Case 2. Electrocardiographic changes before operation, during oral Dibenzyline therapy, and following removal of the tumor. *A*, Preoperative tracing, blood pressure 190/130 mm. Hg. *B*, Preoperative on oral Dibenzyline, blood pressure 150/90 mm. Hg. *C*, Postoperative three days, blood pressure 140/80 mm. Hg. *D*, Six months postoperative, blood pressure 130/80 mm. Hg.

Electrocardiographic description: Unusual electrocardiographic findings were noted preoperatively in this patient, during the administration of adrenolytic agents, and postoperatively. Initial tracings (Fig. 2,A) revealed deep S waves in Leads V_1 and V_2 as well as tall R waves in Leads V_4 and V_5. S-T segment depression and diphasic or inverted T waves were present in Leads I, II, III, aV_L, aV_F and V_3 to V_6. S-T segment elevation with terminal inversion of the T wave was noted in Lead V_2. These changes were interpreted as representing diffuse myocardial ischemia as well as probable left ventricular hypertrophy and, in order to ascertain to what extent the abnormalities might be secondary to circulating pressor amines, all chemodiagnostic tests were performed with simultaneous recording of the electrocardiogram.

Following intravenous administration of benzodioxane, and on another occasion Dibenzyline, reduction of blood pressure resulted and the following changes were noted in the electrocardiogram (Fig. 3 and Fig. 4): (a) a shift to a more vertical position of the heart; (b) clockwise rotation of the heart; (c) a change of the inverted or diphasic T waves in Leads I, II, aV_L, aV_F, and V_3 to a more nearly upright configuration; and (d) a definite prolongation of the Q-T interval from 0.30 to 0.36 sec. following the use of Dibenzyline (Fig. 3,B) despite the increase in cardiac rate from 75 to 136 ($Q\text{-}T_c$ 0.35 prolonged to $Q\text{-}T_c$ 0.52 sec.).

All leads returned to the previous appearance (Fig. 2,A) with the return of the blood pressure to hypertensive levels. The blood pressure elevation following hexamethonium and histamine administration did not produce significant changes in the electrocardiogram.

Preoperative tracings prior to administration of oral Dibenzyline, compared to those obtained during the period of effective adrenergic blockade, revealed a definite shift towards a more vertical heart with clockwise rotation (Figs. 2,A and 2,B). In addition, the previously noted T-wave inversion over the right precordium was no longer present. This may have been related to the change of electrical position.

After removal of the tumor, similar diminution of the T-wave abnormalities was immediately noted (Fig. 2,C) and six months later (Fig. 2,D) further reversion was noted with the T waves in Leads I, II, aV_L, V_4, V_5, and V_6 at that time being diphasic or isoelectric. The tracing had not, however, returned to normal.

Fig. 2.—Case 2. Electrocardiographic changes before operation, during oral Dibenzyline therapy, and following removal of the tumor. *A*, Preoperative tracing, blood pressure 190/130 mm. Hg. *B*, Preoperative on oral Dibenzyline, blood pressure 150/90 mm. Hg. *C*, Postoperative three days, blood pressure 140/80 mm. Hg. *D*, Six months postoperative, blood pressure 130/80 mm. Hg.

REVIEW OF LITERATURE

Electrocardiographic abnormalities were presented in the first case report of a surgically cured pheochromocytoma by Shipley.[13] As subsequent case reports appeared, additional electrocardiographic abnormalities were described and properly attributed to the coexistent chromaffin cell tumors.[14,15] Until 1946, occasional review articles[16-18] appeared in which even more abnormalities were reported and appropriate emphasis was placed on the observation that the presence of a pheochromocytoma could, not infrequently, account for certain abnormal electrocardiograms.

A review of sixty-three case reports of pheochromocytoma[16-52] occurring in the literature since 1946 reveals, however, that the electrocardiogram was not mentioned in thirty-two instances and a normal electrocardiogram was described for only nine patients. Of more significance is the fact that those electrocardiographic changes reported were frequently presented without indication or implication that these abnormalities were related to the pheochromocytoma.

Nonetheless, it is quite apparent from the previous reviews and certain case reports that many different electrocardiographic abnormalities have been recorded which were due to a functioning chromaffin cell tumor. Following the suggestion of MacKeith,[16] these may be categorized as abnormalities of rhythm or abnormalities which suggest myocardial ischemia, damage, or "strain."

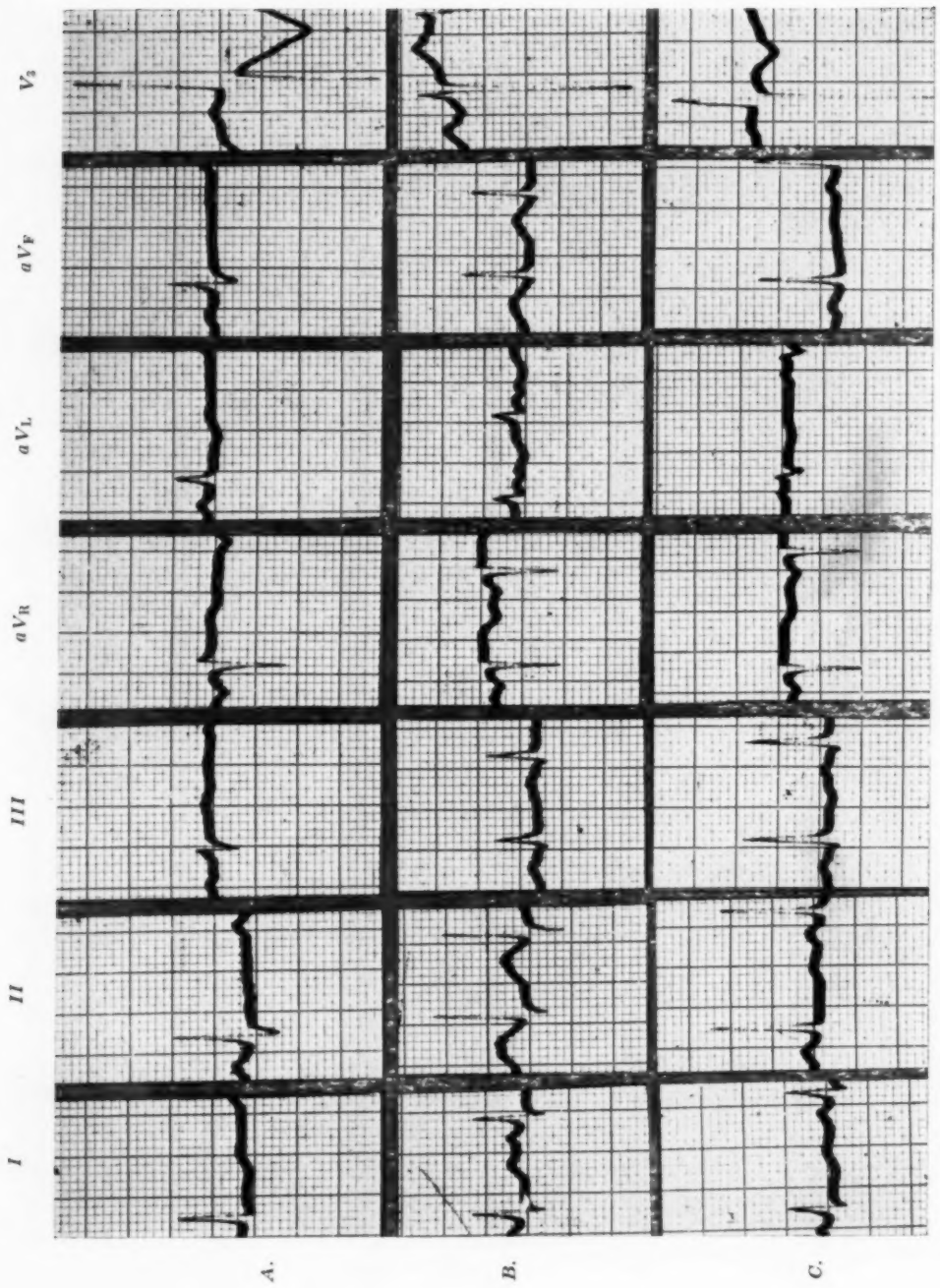

Fig. 3.—Case 2. The effects of intravenous Dibenzyline on the electrocardiographic abnormalities of pheochromocytoma. *A*, Control blood pressure 200/130 mm. Hg. *B*, Ten minutes after 40 mg. intravenous Dibenzyline. Blood pressure 130/80 mm. Hg. (Lead aVL is upside down.) *C*, One hour later, blood pressure 140/92 mm. Hg.

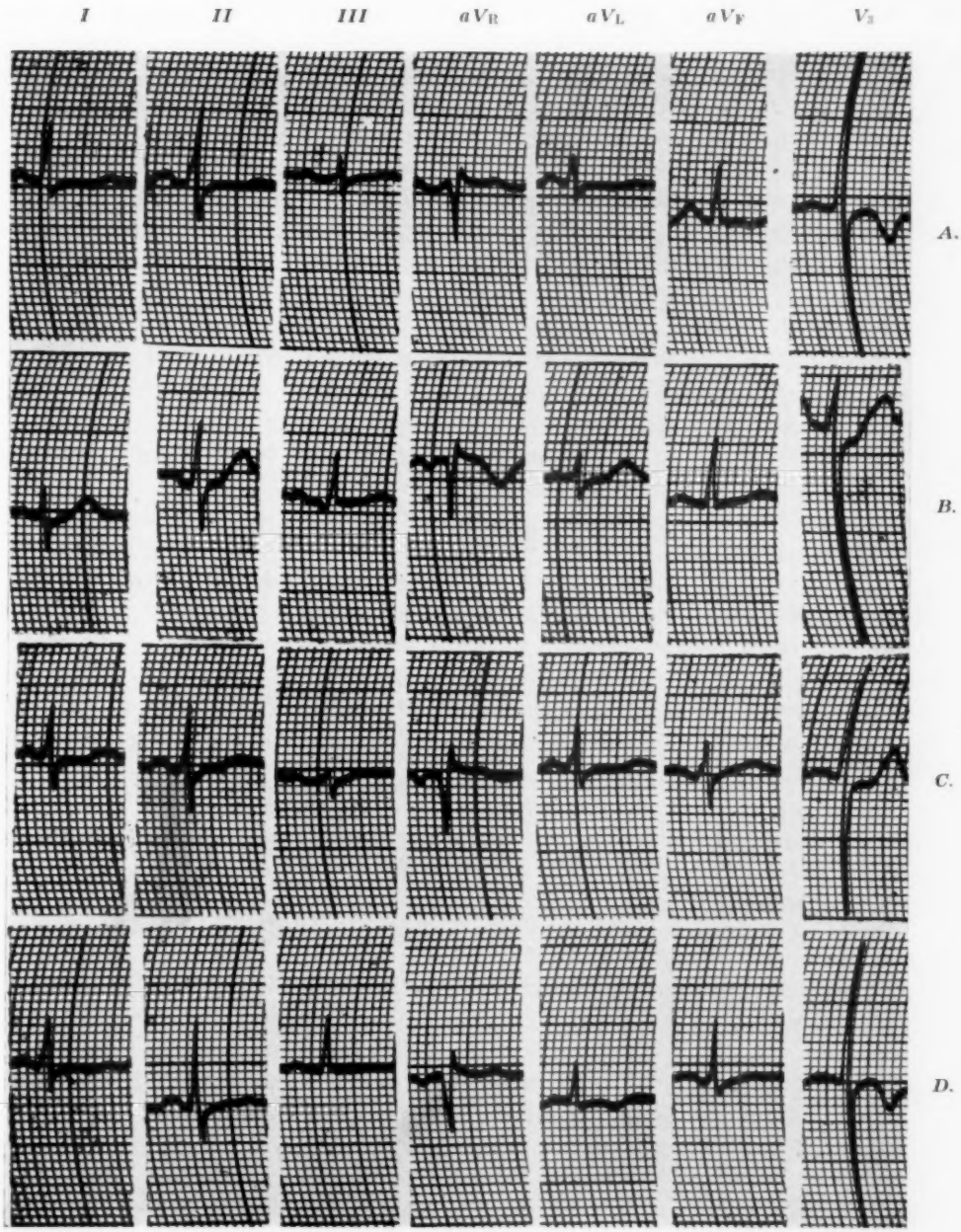

Fig. 4.—Case 2. The effects of intravenous Benzodioxane upon the abnormal electrocardiogram of pheochromocytoma. *A*, Control blood pressure 204/130 mm. Hg. *B*, Eight minutes after 16 mg. Benzodioxane, blood pressure 120/60 mm. Hg. *C*, Twenty minutes later, blood pressure 210/130 mm. Hg. *D*, Eighty minutes later, blood pressure 210/130 mm. Hg.

The abnormalities of rhythm that have been reported are wandering pacemaker,[15] sinoauricular dissociation,[17] auricular tachycardia[2,15] auricular premature contractions,[14,17,44] auricular flutter,[17] auricular fibrillation,[17] nodal tachycardia,[21] ventricular premature contractions,[17,35,35,43] and ventricular tachycardia.[13,35,43] These arrhythmias have occurred most frequently during paroxysms of hypertension[15-18,45] and may persist after the blood pressure has returned to normal levels.[17,43] All reported arrhythmias have disappeared following removal of the tumor. Tetraethylammonium chloride administration has induced cardiac arrhythmia[43] in one patient with a pheochromocytoma, and it would seem possible that electrocardiographic observation of provocative tests for pheochromocytoma might reveal data of value when interpretation of such tests is questionable.

The reported abnormalities suggestive of myocardial damage include right-axis deviation[46] (Cases 1 and 2), left-axis deviation,[14,16,22,23,25,28,44,50,52] abnormally high or peaked P waves,[3,18,21,42,45] low-amplitude or inverted T waves,[14-15,23,24,34,35,42,44-45,52] S-T segment deviation,[21,42,45] (Case 1), and prolongation of Q-T interval[30,52] (Case 1). These changes have occurred transiently during,[15] or between paroxysms of hypertension[21,45] (Case 1) and persistently with sustained hypertension[25,35] (Case 2). Disappearance of these abnormalities prior to the removal of the tumor has occurred spontaneously,[14,16] during hypertensive paroxysms,[21] and during a low-sodium regimen.[45] Partial or complete reversal of this group of changes to normal following removal of the tumor is reported[3,45,53] and well illustrated by our cases. A characteristic of this group, warranting especial emphasis, is the diffuse distribution of the T-wave abnormalities; e.g., inverted T waves in Leads I, II, III, aV_L, aV_F, V_1 through V_6 in our cases and others.[31,35,52]

Undoubtedly the most significant feature of the electrocardiographic abnormalities described above is that demonstrable etiologic factors are most often absent and for this reason clinical suspicion should be directed toward the possibility of a pheochromocytoma.

DISCUSSION

The electrocardiographic abnormalities associated with a pheochromocytoma have previously been attributed to hyperepinephrinemia.[16-18] It is well established that arrhythmias and even cardiac arrest may result from excessive epinephrine administration.[54] This has been attributed to the direct stimulation of the myocardium as well as that stimulation mediated via the conduction tissue.[55] That the arrhythmias arising as a result of epinephrine sensitization can be prevented by adrenergic blockade has also been well documented.[56] There is no evidence, however, that norepinephrine can produce arrhythmias by direct action in the intact normal heart, although elevation of blood pressure alone by this agent may produce sudden changes in cardiac rate and rhythm.[57,58]

Other factors which may contribute to the electrocardiographic changes noted in an adrenalin-secreting tumor may be related to (1) the marked increase in pulmonary artery pressure often produced by epinephrine or norepinephrine[59]; (2) the relatively disproportionate increase in right ventricular work that is

produced by these agents[59] (producing patterns similar to those noted in acute cor pulmonale); (3) the elevation of serum potassium by norepinephrine and lowering by epinephrine.[60,61]

Factors other than hyperepinephrinemia must occasionally be invoked to explain the persistence of diffuse T-wave inversions (Case 2) long after removal of a pheochromocytoma. The reported cases of myocardial infarction[23,34] and autopsy findings of other myocardial pathology[36] attest to the role of organic myocardial damage in the production of some of the abnormal electrocardiographic findings in pheochromocytoma. These persistent changes after tumor removal are uncommon in the reported cases covered by this review. Organic damage may be differentiated from electrocardiographic abnormalities which are produced by excess circulating pressor amine by the administration of adrenolytic drugs as shown in our experience with Case 2.

It is evident from the foregoing discussion that the pathogenesis of the abnormal electrocardiogram produced by a pheochromocytoma is a complex interplay of the relative amounts of epinephrine and norepinephrine secreted by the tumor, the duration of the secretion, whether intermittent or sustained, and the net effects of these pressor amines upon the cardiac rate, rhythm, output, oxygen demand and supply, as well as the coronary circulation, pulmonary and peripheral arterial resistance, and perhaps the body electrolyte distribution.

Evaluation of the changes apparent in our cases would suggest that in Case 1 the S-T segment deviation, prolonged Q-T interval, and diffusely abnormal T waves (Fig. 1,A) were the result of reversible myocardial injury. This seems more logical when one considers the brief periods of hypertension and the complete return to a normal tracing after tumor removal. The marked right-axis deviation which occurred during norepinephrine infusion (Fig. 1,B) may have been a manifestation of the sudden increase of right ventricular work discussed previously since systemic hypertension did not accompany the infusion. The high P waves may have resulted from increased auricular pressure. Serum electrolytes were not determined, but this factor could possibly have influenced the reversion of previously inverted T waves by the norepinephrine infusion.

In Case 2 the sustained hypertension, as well as excessive circulating pressor substances, may have been the responsible factors underlying the diffuse S-T segment deviation and T-wave inversion (Fig. 2,A). Undoubtedly this combination resulted in reversible as well as irreversible myocardial injury. This is supported by the diminution in extent of these abnormalities which followed the administration of the adrenolytic drugs, as well as the observation after operation that the same changes affected by these agents were the ones which disappeared following the removal of the tumor. The changes (Fig. 2,D) which persisted for 6 months must be attributed to diffuse myocardial damage which has been shown at autopsy to have occurred in patients with pheochromocytoma and sustained hypertension.[36]

SUMMARY

1. Two patients with pheochromocytoma and abnormal electrocardiograms due to the presence of this tumor are reported. Serial tracings illustrating the effects of surgery, as well as the administration of adrenolytic agents, are presented.

2. Pertinent literature is reviewed, and it is observed that the association of pheochromocytoma and electrocardiographic abnormalities has been previously noted though recently neglected.

3. The reported abnormalities are either arrhythmias or changes suggesting myocardial damage, ischemia, or "strain." A singularly striking feature of the latter group is the diffuse distribution of the S-T segment and T-wave changes.

4. The role of excessive circulating epinephrine and/or norepinephrine in the production of these changes is discussed.

5. It is emphasized that in the absence of known etiology certain electrocardiographic abnormalities may indicate the presence of a pheochromocytoma.

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THE AORTIC ELECTROKYMOGRAM IN NORMAL SUBJECTS AND PATIENTS WITH SYPHILITIC AORTIC INSUFFICIENCY

MARTIN BRANDFONBRENER, M.D.,* AND HENRY EISENBERG, M.D.**

HOT SPRINGS, ARK.

THE electrokymogram has been used in studying mitral insufficiency,[1] myocardial infarction,[2] constrictive pericarditis,[3] aneurysms of the aorta,[4] insufficiency of aortic and pulmonic valves,[5] as well as ventricular asynchronism.[6] The present study was undertaken to determine the normal values of various phases of the cardiac cycle as measured in aortic electrokymographic (EKY) tracings taken along various positions on the aorta[7] and to compare these with similarly measured values from EKY tracings of patients with syphilitic aortic insufficiency. It was hoped that some idea of the usefulness of this method, either as a clinical or physiologic tool, might be obtained.

METHODS

The tracings were photographically recorded using a Cambridge Simpli-Trol electrocardiograph operated at 2.5 cm. per second. The standard electrokymographic photosensitive tube[8] with "adequate" filter was positioned fluoroscopically. The patients were seated, and the phototube placed at the right border of the ascending aorta, one inch above the upper border of the right auricle. A record of about six beats was made in mid-inspiration. Records were made of the aortic knob similarly. Then, after turning the patient to the 45° left anterior oblique (LAO) position, a record was again made of the ascending aorta one inch above the origin of the aorta. Simultaneous stethographic tracings taken with a crystal pickup microphone placed over the apex of the heart were recorded to be used as a timing device.

In each patient, a tracing of the ascending aorta and the aortic knob was made in the posteroanterior (P-A) position and an ascending aortic tracing in the LAO position. An attempt was made to measure two beats in each record, or six beats per patient, to the nearest 0.01 second. Some records were eliminated because of one or more of the following reasons: too great a variation from one beat to the next; the amplitude of the beats too small for accurate measurement; a wandering base line; respiratory movements; or an unsatisfactory simultaneous stethographic tracing.

From the Public Health Service Medical Center, Hot Springs National Park, Ark.
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*Present address: Section on Gerontology, Baltimore City Hospitals, Baltimore, Md.
**Present address: City Health Department, 18 Municipal Courts Building, 14th and Market Streets, St. Louis, Mo.

The first major deflection of the first heart sound of the stethograph was chosen as the beginning of isometric contraction (line *a*, Fig. 1) which lasted until the onset of a sharp upward deflection of the EKY tracing (line *b*, Fig. 1), at which time the rapid ejection phase was thought to have begun. The peak of the EKY curve (lines *c* or *d*, Fig. 1) was considered to be the end of rapid ejection and the onset of reduced ejection. The latter lasted until the onset of the second heart sound (line *e*, Fig. 1) which was felt to be a more accurate timing point than the position of the notch which was not always clear. Note was made of the contour of the curve and the prominence of the dicrotic notch on the descending limb of the curve. In some abnormal curves, this method of measuring could not be applied and these curves will be discussed separately.

Sixty normal adults whose ages ranged from 17 to 35 years, and thirty-three patients with syphilitic aortic insufficiency whose ages ranged from 40 to 74 years, were studied.

RESULTS

Normal Subjects.—The averages with standard deviations, the number of beats measured, and the number of subjects are shown for each position on the aorta in Table I.

TABLE I. MEASURED VALUES IN NORMAL SUBJECTS

	ASC. AORTA P-A			ASC. AORTA LAO			AORTIC KNOB		
	MEAN SEC.	S. D.	NO. PTS. / NO. BEATS	MEAN SEC.	S. D.	NO. PTS. / NO. BEATS	MEAN SEC.	S. D.	NO. PTS. / NO. BEATS
Isometric	.041	.011	38 / 73	.047	.015	43 / 85	.058	.013	60 / 118
Rapid Ejec.	.097	.035	38 / 73	.101	.049	43 / 85	.139	.039	60 / 118
Reduced Ejec.	.133	.048	38 / 73	.113	.037	43 / 85	.075	.030	60 / 118
Systole	.271	.024	38 / 73	.264	.035	43 / 85	.271	.048	60 / 115
Diastole	.458	.114	38 / 73	.434	.213	43 / 85	.458	.108	60 / 117
Cycle Length	.729	.068	38 / 73	.698	.129	43 / 85	.729	.136	60 / 117

Essentially, the measurements in the various positions are similar except that in the records made from the aortic knob, the duration of the mean isometric contraction and the mean rapid ejection are somewhat longer and the mean reduced ejection is somewhat shorter than in ascending aortic records. The observed difference of the means in isometric contraction between the knob and 45° LAO ascending aortic tracings is 5.5 times its standard error.[9] The observed difference of the means in rapid ejection between the LAO ascending aortic and the aortic knob positions is 5.4 times its standard error. The observed difference of the means in reduced ejection between the LAO ascending aortic and aortic knob records is 7 times its standard error. From Table I, it can be seen that the means of the measured beats are of comparable lengths.

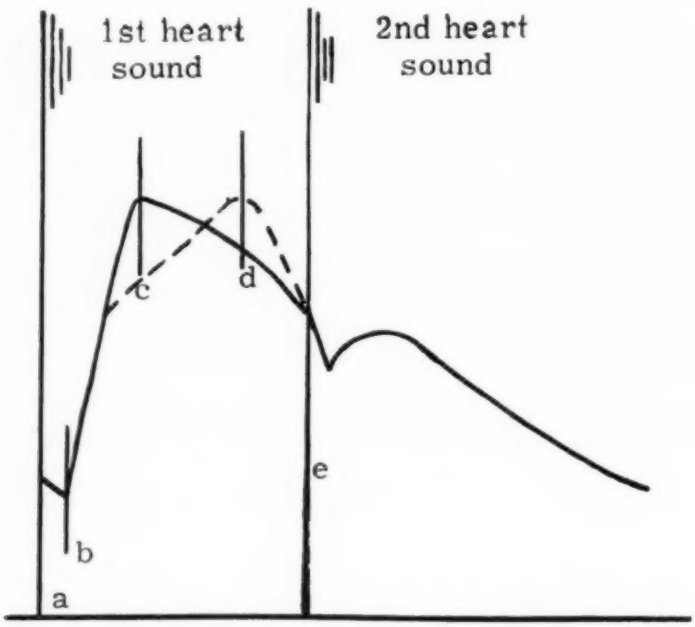


Fig. 1.—See text for description.

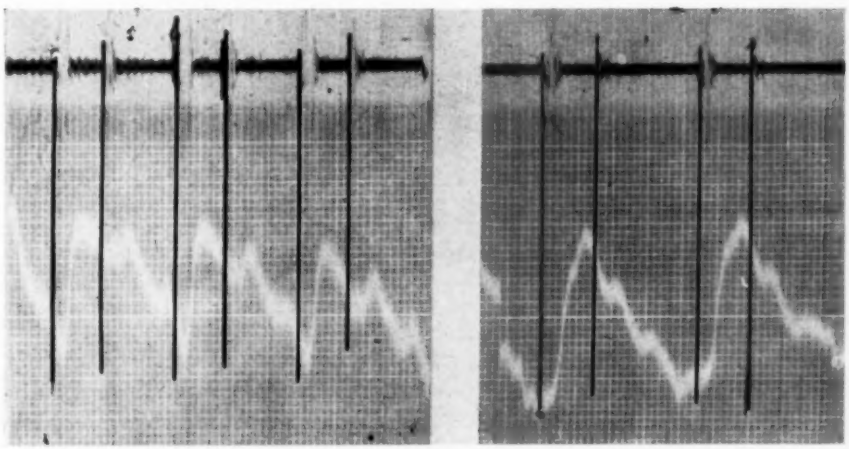
The records were satisfactory for measurement of the ascending aorta in the P-A position in thirty-eight patients (63.4 per cent) of the total number of patients as shown in Table I. In the ascending aortic LAO position, the records of forty-three patients (71.7 per cent) were acceptable. In all sixty patients, the aortic knob records were readable.

The records in normal subjects displayed the following characteristics: the record of the "isometric contraction" period, which includes the lag of the apparatus, was usually horizontal or descending, as shown in Fig. 1 between vertical lines *a* and *b*. In every case, the onset of rapid ejection was marked by a sharp upstroke at line *b* in Fig. 1.

At this point, variations in the normal records are noted in various positions. Two general types of rapid ejection curves are noted. One rises rapidly to its summit (Fig. 2,*A*) and the other rises rapidly, at first, then more slowly (Fig. 2,*B*),

so that a change in direction of the rapid ejection curve occurs. The latter curve, drawn in a dotted line in Fig. 1, has a longer duration of rapid ejection than the former, which is drawn in a solid line in Fig. 1.

Among the thirty-eight satisfactory records of the ascending aorta taken in the P-A position, the more prolonged curve, which changed direction while rising, occurred twice. The other records displayed the rapidly rising curve. Among the forty-three satisfactory records of the ascending aorta in the LAO position, the rapidly rising curve occurred thirty-eight times and the more prolonged rapid ejection curve occurred five times. However, in the aortic knob tracings, the rapidly rising curve occurred thirty-five times, and the more prolonged curve twenty-five times. This might explain the longer duration of rapid ejection in the aortic knob records shown in Table I.



A. *B.*

Fig. 2.—*A*, This is an ascending aortic record of a normal 18-year-old subject. There is a rapid rise and a gradual descent until the second heart sound when the fall becomes faster. There is a prominent dicrotic wave. *B*, This is the aortic knob record of a normal 29-year-old physician. There is a rapid rise at first, then a slower rise with a resultant prolongation of rapid ejection.

After the ejection curve had reached its summit, it fell slowly until the second heart sound (line *e*, Fig. 1) when systole ended. The curve then usually changed direction rather abruptly, falling until the dicrotic notch occurred. The measurement of this interval which should give a value for protodiastole could not be measured accurately enough for this report. Following the dicrotic notch, a dicrotic wave of variable size and shape occurred. Some inconstant vibrations occurred after the dicrotic wave until the next first heart sound, marking the end of diastole. The distinctness of the dicrotic notch depends in part on the presence of a dicrotic wave. The aortic knob tracings were found to have a less prominent dicrotic wave than the ascending aortic tracings in thirty-nine instances, while a more prominent dicrotic wave was found in only four cases. "Absence and diminution of incisural markings" has been described as an abnormal finding.[5] As shown in Table II, an indistinct notch with an imperceptible or barely perceptible change in direction of the curve in its descent was found in eight normal subjects, four in the knob tracing and four in the ascending aortic tracing.

TABLE II. ABSENCE OF DICROTIC NOTCH IN NORMAL SUBJECTS AND PATIENTS WITH AORTIC INSUFFICIENCY

	INDISTINCT NOTCH	POSITION	
		KNOB	ASC. AORTA
Normals No. 60	8	4	4
Aortic Insufficiency No. 33	21	11*	15*

*In 5 patients absence of notch was noted in more than one position.

In all subjects, the sensitivity of the recording apparatus was the same for all positions recorded. Despite this, of the fifty-four records suitable for comparison of the various positions, in forty-seven the knob tracings were of greater amplitude than the ascending aortic records, and in seven the reverse was true.

The measured values in the various positions were tested by the *beta* coefficients to determine the "normality" of the distributions. The standard errors of these coefficients were within acceptable limits so that the readings could be considered as coming from a normally distributed population.

Patients With Syphilitic Aortic Insufficiency.—In Table III, the average measured values with standard deviations, the number of patients, and the number of

TABLE III. VALUES MEASURED IN PATIENTS WITH SYPHILITIC AORTIC INSUFFICIENCY

	ASC. AORTA P-A			ASC. AORTA LAO			AORTIC KNOB		
	MEAN SEC.	S. D.	NO. PTS. / NO. BEATS	MEAN SEC.	S. D.	NO. PTS. / NO. BEATS	MEAN SEC.	S. D.	NO. PTS. / NO. BEATS
Isometric	.034	.012	17 / 33	.032	.009	13 / 26	.063	.029	31 / 61
Rapid Ejec.	.099	.053	17 / 33	.099	.049	13 / 26	.145	.040	31 / 61
Reduced Ejec.	.174	.066	23 / 46	.167	.056	17 / 34	.089	.037	31 / 61
Systole	.300	.045	23 / 46	.288	.038	17 / 34	.297	.039	31 / 61
Diastole	.457	.127	23 / 46	.411	.135	17 / 34	.448	.135	31 / 61
Cycle Length	.756	.159	23 / 46	.702	.159	17 / 34	.744	.161	31 / 61

beats measured are shown. The values in the various positions show relations to each other similar to the normal group; that is, the mean isometric contraction and mean rapid ejection phases are longer and the mean reduced ejection phase shorter in the aortic knob as compared to the ascending aortic tracings. The observed differences of the means between the knob and 45° LAO ascending aortic tracings are 7.7, 4, and 7 times, respectively, the standard error of the differences.[9]

Comparison of the values in Table III with those in Table I reveals a shorter isometric contraction phase in the aortic insufficiency patients in the ascending aortic positions. The observed difference of the means between the ascending aortic tracings in the normal subjects and the aortic insufficiency patients in the 45° LAO position is 6 times the standard error of the difference and is beyond the 1 per cent level by analysis of variance. However, beat-to-beat variations in any one patient make the observed differences in the isometric contraction phase in the other positions not significant.

The rapid ejection phases are similar in duration in the aortic insufficiency patients and normal subjects. The mean reduced ejection phase is significantly longer in the aortic insufficiency patients in all positions. The observed differences between the mean values in normal subjects and aortic insufficiency patients in the ascending aorta, P-A and LAO, and the aortic knob are respectively 3.7, 5.4, and 2.5 times their standard errors,[9] and at 1 per cent, 1 per cent, and 5 per cent levels of significance by analysis of variance. The increased mean total systole is due, therefore, to an increase in the mean reduced ejection phase.

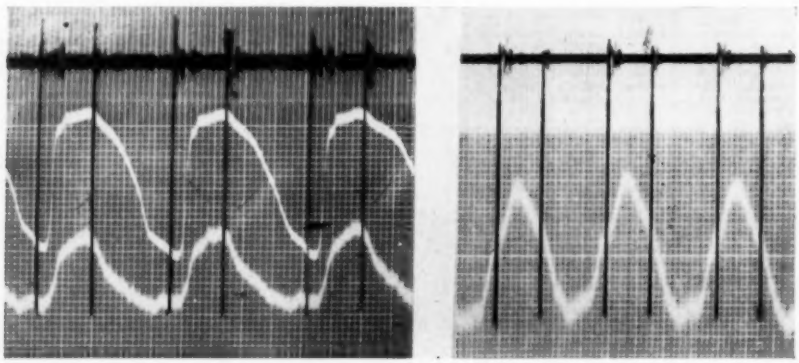
From Table III it can be seen that of thirty-three patients with aortic insufficiency, between thirteen and twenty-three had satisfactory records of the ascending aorta in various positions, while thirty-one patients had satisfactory aortic knob records.

The contour of many of the aortic insufficiency records was similar to the normal records. The isometric contraction phase was most frequently horizontal or descending. In seven patients, in the ascending aortic tracing, the isometric contraction phase rose after the first sound so that a clear demarcation between isometric contraction and rapid ejection could not be made. This never occurred in aortic knob tracings or in records of normal subjects in any aortic position.

Four general types of curves were noted. Two have been described in the normal subjects. One is the "rapidly rising" curve (Fig. 2,*A*); another is the more slowly rising with prolonged rapid ejection (Fig. 2, *B*); and the third, which is seen in the patients with aortic insufficiency and not in those who were normal, was characterized by a very rapid systolic rise and a rapid sharp descent before the second heart sound, as shown in Fig. 3, *B*. The tracing usually continued to fall after the second heart sound with little or no dicrotic wave. Toward the end of diastole, this curve rose sharply until the next first heart sound. This type of curve was seen frequently in the ascending aortic records, but only twice in aortic knob records.

The last type of curve seen in some records was not measurable because it did not conform to an aortic contour. These curves were marked by a rapid descent soon after the first heart sound, which rose after the second heart sound.

This is referred to as the ventricular-type of curve which it strongly resembles.[2] This occurred in the P-A ascending aortic record in eight patients and in the 45° LAO position on the ascending aorta in five patients. As shown in Table IV, it never occurred in aortic knob records or in the normal subjects. The significance of these records will be discussed later.



A. *B.*

Fig. 3.—*A*, This is the aortic knob record of a 74-year-old patient with syphilitic aortic insufficiency. The lower curve is the EKY, the upper curve the carotid tracing. The stethogram is uppermost. There is at first a rapid rise, then a slower rise. There is no dicrotic wave visible. *B*, This is an ascending aortic tracing of a 56-year-old patient with syphilitic aortic insufficiency. There is a rapid rise after the first heart sound, and a rapid descent which continues well into diastole.

In Table IV, the number of records in each category, present in each aortic position, is shown. The contour of more records is described in Table IV than is shown in Table III, because some records were distinct as to contour, but not measurable because of poor stethograms or blurring of the record.

TABLE IV. FREQUENCY OF VARIOUS TYPES OF CURVES IN PATIENTS WITH AORTIC INSUFFICIENCY

	ASC. AORTA		AORTIC KNOB
	PA	LAO	
1. Rapid rise	7	7	21
2. Rapid then slower rise with more prolonged rapid ejection	2	4	9
3. Rapid rise with rapid fall	13	10	2
4. Ventricular type	8	5	0

In Table II, the high incidence of an absent or barely perceptible dicrotic notch is compared to the presence of this finding in normal subjects. In twenty-one of thirty-three aortic insufficiency patients this was found, though often in just one position on the aorta, and a record with this finding is shown in Fig. 3,*A*.

In the normal records, the amplitude of the knob in forty-seven of fifty-four patients was greater than the amplitude of the ascending aortic records. In aortic insufficiency, the knob records were of greater amplitude in ten of thirty-three patients, smaller in thirteen of thirty-three, and about the same size in ten records.

There was no correlation noted between the contour of curves in aortic insufficiency and the pulse pressure or diastolic pressure, measured by the auscultatory method.

DISCUSSION

In evaluating the results presented, certain fundamental concepts must be considered. The tracings obtained by this method are of movements of the aorta in one direction only. They are records of movements of structures surrounded by pulmonary tissue, encased in the chest. They are recorded with a phototube and filter system having a constant and definite lag. Artifacts of positional movement of the vessel, rather than intrinsic expansion and contraction, must be taken into consideration in evaluating an individual record. Artifacts due to improper positioning of the phototube must be considered. For example, pulmonary hilar pulsations may be recorded when it is believed that aortic tracings are being made. Artifacts in timing due to asynchronism must be borne in mind. In exploring a new method such as this, the differentiation of the artifact from a significant record is at times difficult. One has recourse to certain physiologic data, obtained by using a different method, to support the significance of electrokymographic records. Aortic pressure curves have often helped to decide the significance of an EKY record. There are difficulties in using pressure curves as "models", since electrokymographic records depend not only on changes in intraluminal pressure, but on the physical characteristics of the wall of the vessel and surrounding tissues and also on the distortion introduced by the recording device.

The differences in the age groups studied must also be borne in mind. The control group was composed of young healthy adults; the oldest was 35 years of age. The patients with aortic insufficiencey were all over 40 years of age. The results of measurements in normal subjects compare well to those previously published,[7] considering differences in cycle lengths in the two series. No previous measurements have been published of aortic insufficiency records.

The results reveal that in normal patients the mean isometric contraction and rapid ejection periods are both somewhat longer in the aortic knob records than in the ascending aortic records, with a resultant shortening of the mean reduced ejection period in the knob tracings. The lag introduced by the recording tube and filter is, of course, the same for both sets of records. If it is assumed that the distance between the ascending aortic position and the aortic knob position is eight inches, and if the pulse wave velocity is assumed to be 10 meters per second, then the delay time would be 0.02 second. This may be the explanation of the apparent increase of the mean "isometric contraction" phase.

A prolongation of mean rapid ejection in the knob tracing, as compared to the ascending aortic tracing, may be explained by reference to the contour of the curves in the various aortic positions. The contour of the ascending aortic

curves is most frequently that of a rapid rise, while the aortic knob records frequently display a bend or change of direction in the ascending limb, which is associated with a more prolonged rapid ejection.

The significance of these two types of normal curves is unknown. The normal pressure curve, as described by Wiggers[10] in its anacrotic limb, shows a gentle bend until the summit is reached, then a gradual decline until the incisura. The assumption may be made that the differences observed between the pressure curve and the EKY curve are due to damping and distortion of this pressure curve by recording it through the aortic wall, which is surrounded by mediastinal structures, lung tissue, etc. A certain degree of distortion may be introduced by the recording apparatus. It is well known that intraluminal pressure curves change as one progresses centrifugally in the arterial system. There is usually not too great a transformation of pressure pulse contour between the ascending aorta and the aortic knob, except some "rounding off" of contour and changes due to summation or resonance of reflected waves.[11] The latter may possibly explain the different types of normal curves.

The explanation of the greater amplitude of the knob tracings seems most probably associated with the fact that the knob is less fixed than the root of the aorta and able to respond to the impact of the ejected blood with a greater excursion. In the records of both normal patients and those with aortic insufficiency, the percentage of readable records is higher in the aortic knob position. Placing the phototube accurately is a simpler matter there, since the aortic knob moves more freely and is not adjacent to the pulmonary hilum, spine, and vena cava, all of which can cause unsatisfactory "aortic" curves.

In the aortic insufficiency tracings, durations of the phases of the cardiac cycle in the aortic knob, as compared to the ascending aortic records, were similar to those of the normal subjects; namely, a longer mean isometric contraction period and rapid ejection period and a shorter mean reduced ejection period in the knob tracings. The explanation offered for this is the same as that offered for the normal records.

A shorter mean isometric contraction phase was noted in the aortic insufficiency records of the ascending aorta as compared to normal records. This proved to be statistically significant after analysis of variance in only the 45° LAO position. A prolonged isometric contraction phase is seen in intraventricular records in experimental aortic insufficiency.[12] It occurs almost immediately after production of experimental aortic insufficiency and accompanies the increased initial tension and steeper rise of the intraventricular pressure curve if the leak is very large.[12]

A statistically significant increase in the mean reduced ejection was noted in aortic insufficiency records. This accounted for an increase in the total mean systole, despite the mean rapid ejection remaining essentially the same.

The mean length of systole is longer in aortic insufficiency records than in the records of the normal subjects. Analysis of variance reveals that this prolongation is not statistically significant. These small increases in length of systole, however, might suggest an increased diastolic heart size.[11] The patients in this study were clinically compensated, although many were receiving digitalis and had been in congestive heart failure.

The contour of the records in aortic insufficiency patients remains to be explained. In some records of the ascending aorta, but not the knob, a record resembling a ventricular record was obtained. These could not be measured as were the aortic tracings and are not included in the averages shown in Table III. This type of tracing never occurred in normal subjects. Either the phototube was misplaced or the ascending aorta, at its emergence from the right heart border as seen fluoroscopically, displayed a positional movement which overshadowed the intrinsic movement of the aorta. In five patients this type of curve appeared in the P-A and the LAO tracings, indicating a greater probability of the second suggestion applying in these cases.

A large number of the tracings were similar to those obtained in normal subjects. However, a curve marked by a steep rapid ascent and a steep decline to the base line (Fig. 3,*B*) before the second heart sound with a continued downward movement in diastole was often seen in the ascending aortic tracings in aortic insufficiency (Table IV). This would seem to resemble the "systolic collapse" described for pressure tracings in experimental aortic insufficiency.[12] However, a positional movement of the root of the aorta, as a cause of this contour, has not been excluded. This never was seen in normal subjects and rarely in the knob tracings of aortic insufficiency patients. This "systolic collapse" never was seen except in the records with a short steep anacrotic rise.

The loss of a dicrotic wave was seen in 64 per cent of aortic insufficiency patients. It has been described in experimentally produced aortic insufficiency and explained by Alexander as due to an elimination of the aortic standing wave, primarily due to the creation of the wide aortic opening which destroys the resonant property of the arterial system.[13] This finding was noted in some normal patients. In these, and probably in some of the patients with aortic insufficiency, the most likely explanation is that dicrotic waves were absent because of the damping of the curve by the aortic wall and possibly because of inherent defects of this method of recording border movements.

While there are differences of a fairly marked degree between aortic insufficiency records and normal records, in contour more than in measurements, there is no typical record of aortic insufficiency which invariably occurs in that condition and no other condition. The changes in the timing of reduced ejection is statistically significant, but a considerable degree of overlap exists, and beat-to-beat variations prevent making a diagnosis from observation of a single tracing.

By the use of the prolongation of the reduced ejection phase in positions and IV, which is the most obvious measurement difference between normal subjects and patients with aortic insufficiency, the EKY is only 40 per cent specific in detecting this prolongation, while 5 per cent of normal subjects would have a similar prolongation.

The present instrument cannot be calibrated as to amplitude. It is well known that a high systolic pressure, low diastolic pressure, and therefore a wide pulse pressure, exist in aortic insufficiency. However, in these tracings the amplitudes of various records cannot be compared. There is also some doubt as to the linearity of response along various parts of the slit of the phototube. The very nature of recording through so many surrounding structures introduces damping

errors which might confuse the interpretation of records. Thus, the interpretation of any single record is still very unsatisfactory, and the statistical, empiric approach is at present the only method available. As a clinical method in studying the aorta, the EKY would seem to be extremely limited. As a physiologic tool, it is crude and certainly would benefit from improvements that would permit calibration for comparison of amplitudes.

CONCLUSIONS AND SUMMARY

Aortic electrokymographic records were made from the ascending aorta in the P-A and LAO positions and from the aortic knob in sixty normal subjects and thirty-three patients with syphilitic aortic insufficiency.

The knob records in both groups of patients showed a slight increase in the mean measured "isometric contraction" and mean rapid ejection phases, with a resultant decrease in the mean reduced ejection phase when compared with the ascending aortic records.

In the patients with aortic insufficiency, a prolonged reduced ejection phase was noted.

In both groups, records from the ascending aorta often were unsatisfactory. The contour of the normal aortic EKY curve was described, and its presence in many patients with aortic insufficiency was noted.

In many patients with aortic insufficiency, a rapidly rising curve with a "systolic collapse" was noted in the ascending aortic records.

The incidence of an indistinct dicrotic notch was compared in normal subjects and in the aortic insufficiency patients and found to be higher in the latter.

A comparison of the amplitude of the various positions recorded from the aorta revealed a higher amplitude in the knob tracings in the normal subjects. This was less often seen in patients with syphilitic aortic insufficiency.

It was noted that measurements of the phases of the cardiac cycle, different from the normal subjects, were not invariable in patients with aortic insufficiency. While a curve is described in aortic insufficiency records which is not seen in normal subjects, no statement can be made at present concerning the specificity of the contour of this curve.

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VENTRICULAR FUNCTION

III. The Pathologic Physiology of Acute Cardiac Tamponade Studied By Means of Ventricular Function Curves

James P. Isaacs, M.D.,* Erik Berglund, M.D.,** and Stanley J. Sarnoff, M.D.***

Boston, Mass.

THERE are two main schools of thought concerning the fundamental circulatory defect in acute cardiac tamponade. One was introduced by Cohnheim in 1889.[1] "Immediately on the establishment in the pericardium of a positive tension of a few mm. Hg, an obstacle is opposed to the entrance of blood from the systemic veins, which. . . . diminishes the quantity of blood flowing into the heart. It is not by interfering with the expansion of the chambers in diastole that the tension of the pericardium brings about the circulatory disturbances." This concept is currently supported by Beck.[2] Starling repeated Cohnheim's tamponade experiments and in 1897 stated the second concept, namely, that there is a ". . . hindrance to diastolic expansion" of the heart.[3]

The purposes of this study were (1) to ascertain whether the primary defect in acute cardiac temponade is an obstruction to venous inflow due to constriction of the entrance orifice, or an interference with diastolic expansion of the ventricles, (2) to examine whether, in the tamponade state, the heart follows Starling's law, (3) to examine the significance of the pressure-volume relationship of the pericardium and the ventricles, (4) to demonstrate the importance of determining the effective ventricular filling pressure, (the pressure inside the heart minus the pressure outside the heart) in interpreting the circulatory compromise encountered in tamponade, and (5) to investigate the effects of increasing the blood volume upon cardiovascular hemodynamics during tamponade. A preliminary report has been presented elsewhere.[4]

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*Formerly, Research Associate, Department of Physiology, Harvard School of Public Health, Boston, Mass. Present address: Department of Surgery, Johns Hopkins Hospital, Baltimore, Md.

**Research Associate, Department of Physiology, Harvard School of Public Health, Boston, Mass.

***Associate Professor, Department of Physiology, Harvard School of Public Health, Boston, Mass.

METHOD

Mongrel dogs weighing between 16.2 and 25.2 kilograms were anesthetized with morphine-chloralose-urethane and maintained on positive pressure breathing. Some of the methods used in these experiments have been described in detail.[5] Briefly, they involve the continuous registration of systemic blood flow (cardiac output minus coronary flow), right and left atrial and pulmonary artery and aortic pressures. From these data the stroke work for each ventricle was calculated over a wide range of filling pressures and during varying degrees of tamponade, and right and left ventricular function curves were constructed (Figs. 4 and 5). The pericardium remained intact except for placement of a perforated metal cannula through which the pericardial pressures were measured. The tip of this cannula was covered by a soft rubber tube to diminish the risk of effusion and bleeding. All pressures were recorded by Sanborn Electromanometers[6] and systemic blood flow was recorded with the Potter* Electroturbinometer.[7,8]

Right and left effective ventricular filling pressures were obtained by subtracting intrapericardial pressure in late diastole from right and left mean atrial pressures, respectively.

Cardiac tamponade was produced by injecting a known amount of air into the pericardial space. In two experiments saline was used instead.

Pressure-volume measurements of each ventricle in the post-mortem dog heart were carried out in the following manner. Immediately after the heart beat ceased, double lumen cannulae were tied into the pulmonary artery and aorta with their ends inside the right and left ventricles, respectively. Clamps were placed firmly across the atrioventricular rings and the heart was then emptied as completely and rapidly as possible. Saline was injected simultaneously into the two ventricles in equal increments of 2 to 5 c.c. at ten-second intervals, and then aspirated in equal decrements at similar intervals while pressures were measured (Fig. 2,*A*).

For the pericardial pressure-volume determinations, the heart was emptied and the great vessels were ligated at the pericardium. Known amounts of fluid were then serially injected and withdrawn through a pericardial cannula, while pericardial pressures were recorded through a side vent. The volume occupied by the heart and intrapericardial portions of the great vessels was then determined by Archimedes method[9] and used as the starting point on the pericardial pressure-volume curve (Fig. 2,*B*).

RESULTS

Fourteen successful experiments were obtained in six dogs.

1. *Hemodynamic Effects of Acute Cardiac Tamponade.*—These are shown in Fig. 1. At the beginning of the signal, 130 c.c. of air were rapidly injected into the pericardium. The pericardial pressure rose from 1.5 to 17 cm. H_2O.

*The authors gratefully acknowledge the assistance of Mr. David M. Potter, Potter Aeronautical Company, Newark, New Jersey.

Right and left atrial mean pressures rose from 9 and 11 cm. H_2O to 20 and 21 cm. H_2O, respectively. Mean aortic pressure fell from 150 to 60 mm. Hg, and mean pulmonary artery pressure fell from 32 to 24 cm. H_2O. Systemic blood flow fell from 3.1 to 1.2 liters per minute. After removal of the air, the values returned to the control levels. This type of experiment was done nine times in six dogs with results similar to those shown.

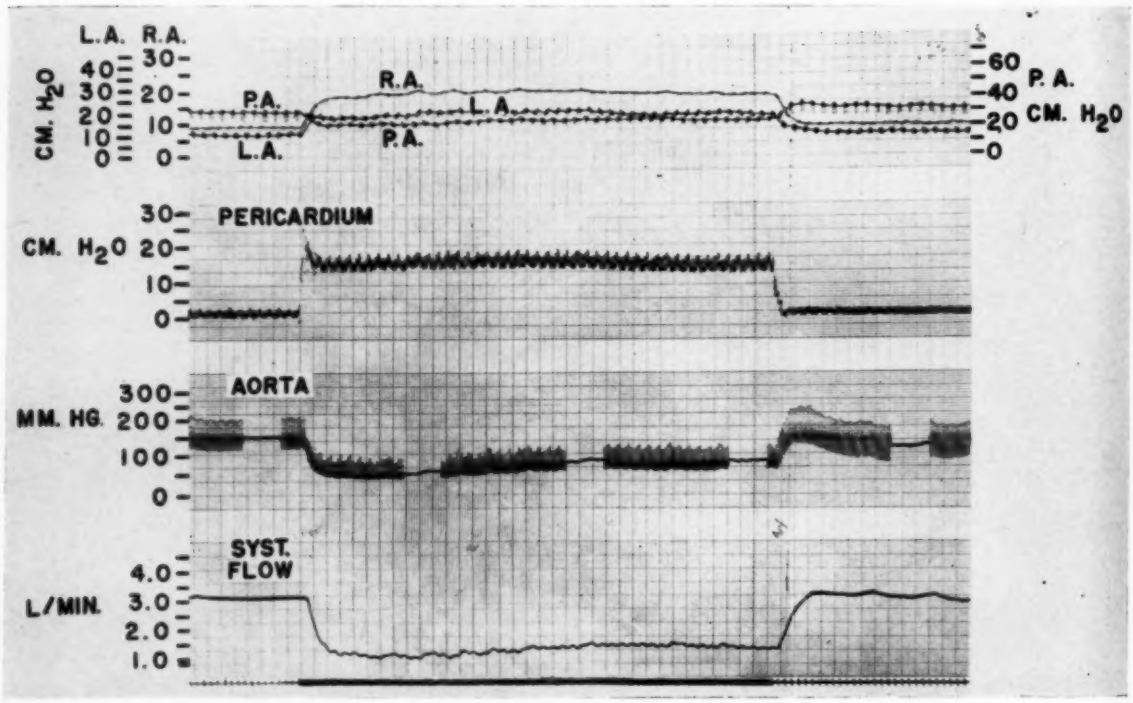
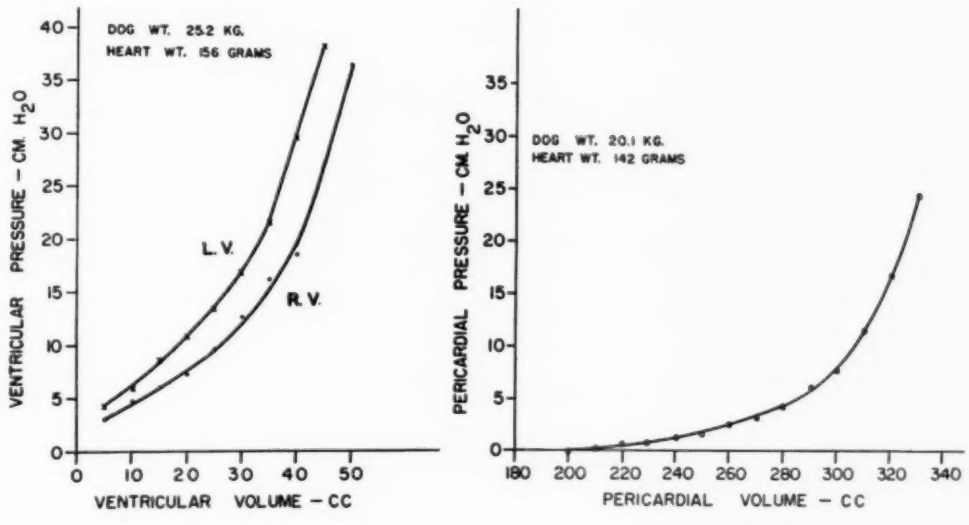


Fig. 1.—Exper. No. 59. Dog weight 20.1 kg. Heart weight 142 grams. Vagi intact. Tracing of hemodynamic effects of acute cardiac tamponade. *P. A.* = mean pulmonary artery pressure (scale at right). *L. A.* = mean left atrial pressure (scale at left). *R. A.* = mean right atrial pressure (scale at left). Aortic pressure is intermittently full pulse pressure and integrated mean pressure. *Syst. Flow* = cardiac output minus coronary flow. Time signal = 1 second. 130 c.c. air injected into the pericardium at beginning of signal and removed at end of signal. See text.

2. *Venoatrial Pressure Gradient With and Without Tamponade.*—In two experiments the pressure gradients were examined across both the systemic and pulmonary venoatrial junctions with and without acute tamponade. Inferior vena caval and right atrial catheters were connected to the same manometer by a three-way stopcock. The pulmonary venous and left atrial catheters were connected to another manometer in the same way. By manual switching of the three-way stopcocks, recordings of venous and atrial pressure on both sides of the heart were obtained in rapid succession. A pressure gradient between the central vein and its respective atrium was not observed either in the control or in the severe tamponade state. The manometric systems as used would clearly reveal differences of as little as 0.2 cm. H_2O if these had occurred.

3. *The Pericardial and Ventricular Pressure-Volume Relationships.*— Fig. 2,*A* illustrates the contour of the post-mortem pressure-volume curves of a 25.2 kilogram dog's right and left ventricles. Fig. 2,*B* is the curve of a 20.1 kilogram dog's pericardium. The pressure increments accompanying given volume increments describe an increasingly steep ascent in each instance. At the lower part of the pericardial curve, substantial increases in volume are associated with only small pressure rises. Here, either relatively large amounts of fluid (or air) may be placed within the pericardium, or the heart volume may increase with little if any counteracting pericardial pressure. When the pericardium is further distended, it reaches a range above which even a small increase in volume produces a large increase in pressure. In this range the intrapericardial pressure becomes an increasingly significant force to overcome in order for the ventricles to expand during diastole.



A. *B.*

Fig. 2.—*A*. Exper. No. 25. Pressure volume curves of left ventricle (*L. V.*) and right ventricle (*R. V.*). *B*, Exper. No. 59. Pressure volume curve of pericardium; the volume of the heart and intrapericardial portions of vessels was 180 c.c.

It is felt that the pericardial pressure-volume relationship is accurately described in Fig. 2,*B*. However, the pressure-volume curves of the ventricles must be considered a crude approximation because of the probable changes of myocardial tone in the post-mortem state.

4. *The Hemodynamic Consequences of Serial Injections of Air into the Pericardium.*—This is shown in Fig. 3. With increasing tamponade the mean atrial pressures rose while the effective filling pressures fell. It is important to note that the stroke work of the ventricles followed the downward trend of the effective filling pressures instead of the upward trend of the atrial pressures.

Each reduction of effective filling pressures became more pronounced with each 10 c.c. injection of air, demonstrating the increasingly steep rise of the pressure-volume curve of the pericardium shown in Fig. 2,*B*.

The decrements in stroke work are relatively large even with small decrements in effective filling pressures, because the ventricles are operating on the steep part of their function curves where small decreases in effective filling pressure produce large decreases in ventricular stroke work.[5]

This type of experiment was performed seven times in three dogs with results similar to those shown.

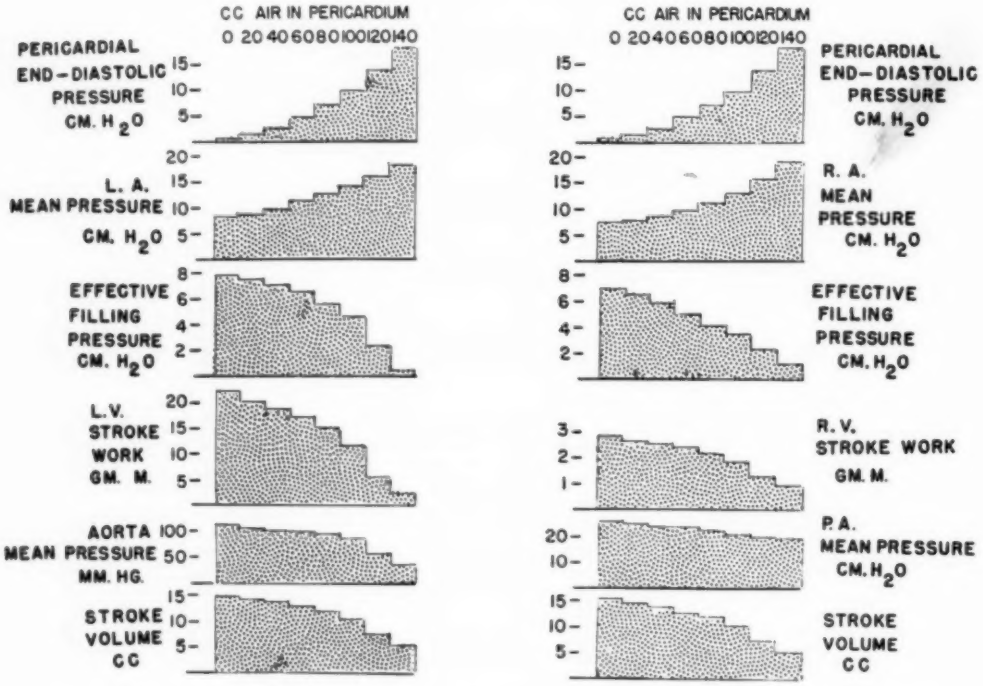


Fig. 3.—Exper. No. 59, same as in Fig. 1. Hemodynamic effects of serial injections of air in 20 c.c. increments into the pericardium. Note that the stroke work of both ventricles follows the trend of the effective filling pressures (atrial minus pericardial pressure), not that of the atrial pressures.

5. *The Effect of Tamponade on the Right and Left Ventricular Function Curves.*—Ventricular function curves were obtained (a) before tamponade, (b) during tamponade of varying degrees, and (c) after removal of the tamponade. A representative set of ventricular function curves are shown at the top of Fig. 4. Also shown are the effects of tamponade on arterial pressures and stroke volumes. The control curves before and after the release of the tamponade (open circles and triangles) are the same. The curves obtained after the injection of 35 c.c. of air into the pericardium (filled circles) are suppressed. With 70 c.c. of air in the pericardium (crosses) this effect is more pronounced.

Seven experiments of the type shown in Fig. 4 were performed in six dogs. The response in each experiment was similar to that shown.

6. *The Difference Between Ventricular Function Curves Plotted With Apparent Filling Pressures and Effective Filling Pressures.*—Fig. 5 shows eight ventricular function curves obtained on the same dog with seven degrees of tamponade (0 to 140 c.c. of air in the pericardium). The broken lines represent the apparent function curves, i.e., ventricular work plotted against mean atrial pressure. The unbroken lines represent the true function curves, i.e., ventricular work plotted against effective filling pressure (mean atrial pressure minus pericardial pressure). While the apparent ventricular function curves show a wide spread with the varying degrees of tamponade, the true ventricular function curves describe different segments of approximately the same curve. It seems clear that when the pressure outside the heart is varied, the effective filling pressure rather than the uncorrected filling pressure is the significant determinant of diastolic fiber length and ventricular work.

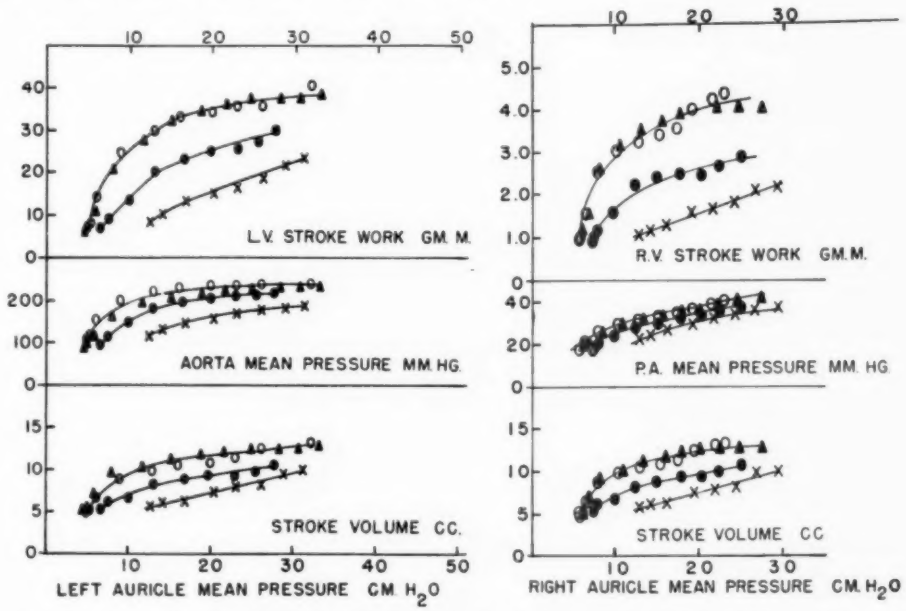

L.V. STROKE WORK GM. M.
AORTA MEAN PRESSURE MM. HG.
STROKE VOLUME CC.
LEFT AURICLE MEAN PRESSURE CM. H2O
R.V. STROKE WORK GM.M.
P.A. MEAN PRESSURE MM. HG.
STROKE VOLUME CC.
RIGHT AURICLE MEAN PRESSURE CM. H2O

Fig. 4.—Exper. No. 34. Dog weight 20.4 kg. Heart weight 226 grams. Vagotomized. Effect of acute cardiac tamponade on simultaneous left and right ventricular function curves (top). Also shown are arterial pressures and stroke volumes plotted against mean left and right atrial pressures. Open circles and triangles = control curves. Closed circles = curve with 35 c.c. air in pericardium. Crosses = curve with 70 c.c. air in pericardium.

7. *The Effects of Increasing Blood Volume in the Dog With Varying Degrees of Tamponade.*—Fig. 6 shows the hemodynamic effects of serially increasing tamponade before and after infusions of 100, 300 and 500 c.c. of blood in a 20.1 kilogram dog. A comparison of these curves shows that increasing the blood volume elevates aortic pressure and cardiac output significantly in mild to moderate tamponade but produces little improvement when tamponade is severe. Infusion elevates atrial pressures by approximately the same amount in all degrees of tamponade even though atrial pressures are at much higher levels when tamponade is severe.

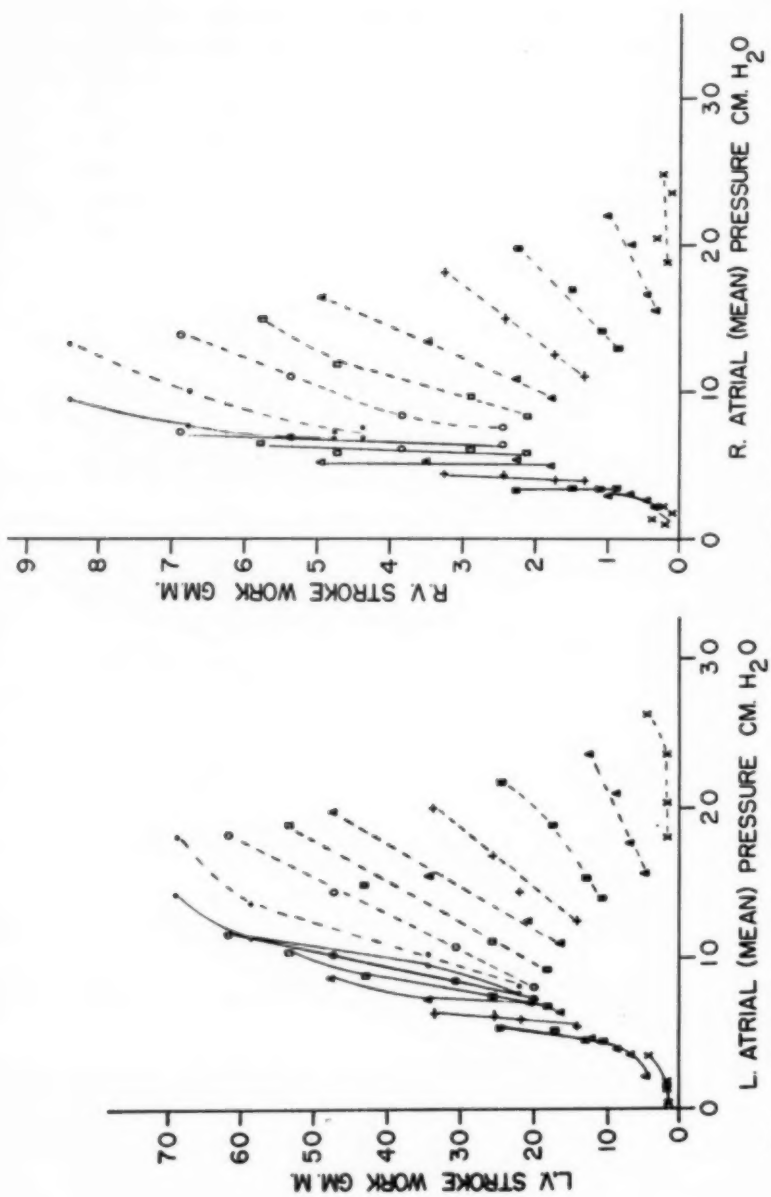


Fig. 5.—Exper. No. 59, same as in Fig. 1. Comparison of apparent ventricular function curves (broken lines) and true ventricular function curves (unbroken lines) obtained during different degrees of tamponade. In the apparent function curves stroke work is plotted against mean atrial pressure, as in Fig. 4. In the true function curves stroke work is plotted against effective filling pressure (atrial pressure minus pericardial pressure). Dots = control. Open circles = 20 c.c. air in pericardium. Open squares = 40 c.c. air. Open triangles = 60 c.c. air. Crosses = 80 c.c. air. Solid squares = 100 c.c. air. Solid triangles = 120 c.c. air. X's = 140 c.c. air in pericardium. Note that the true ventricular function curves are segments of approximately the same curve. See text.

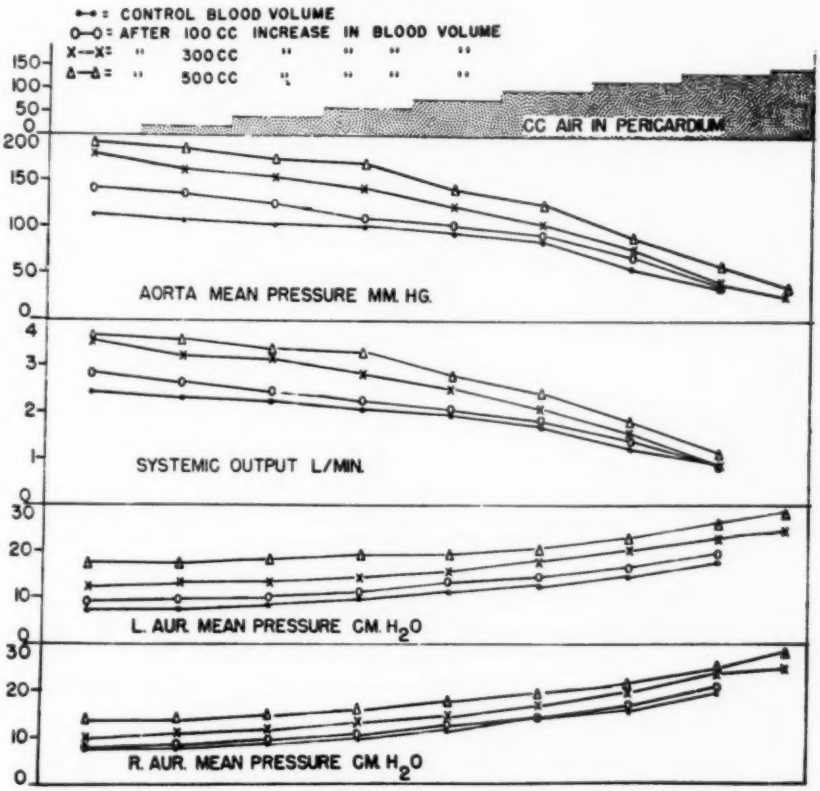

•—• = CONTROL BLOOD VOLUME
O—O = AFTER 100 CC INCREASE IN BLOOD VOLUME
X—X = " 300 CC " " " "
Δ—Δ = " 500 CC " " " "
CC AIR IN PERICARDIUM
AORTA MEAN PRESSURE MM. HG.
SYSTEMIC OUTPUT L/MIN.
L. AUR. MEAN PRESSURE CM. H2O
R. AUR. MEAN PRESSURE CM. H2O

Fig. 6.—Exper. No. 59, same as in Fig. 1. Effect of increasing blood volume with varying degrees of tamponade. Note that in mild tamponade (at the left in figure), increasing the blood volume elevates arterial pressures and cardiac output significantly and in severe tamponade (at the right in figure) there is no significant improvement with increased blood volume.

DISCUSSION

The fact that the pressure gradient across the venoatrial orifice was less than 0.2 cm. H_2O both in the normal and tamponade state indicates that the hypothesis of venoatrial obstruction is not tenable as an explanation of the circulatory defect in tamponade.

Metcalfe and associates[10] made the first full and detailed observations on the hemodynamic consequences of acute cardiac tamponade in the intact dog and the reader is referred to their publication for the pertinent literature. They found that left as well as right atrial pressure rose while cardiac output and pulmonary and femoral artery pressures fell. They state, however, that ". . . the mechanism by which pericardial effusion decreases cardiac output is not yet clear." The data presented above not only amply confirm their findings but also help to explain the most important physiologic consequence of tamponade, namely, the restricted cardiac output.

Taken together with Starling's law of the heart,[5,11] the pressure-volume curve of the pericardium explains the cardiovascular consequences of acute tamponade. The preceding observations demonstrate that the circulatory defect is brought about by a limitation of the pericardial space available for the diastolic expansion of the ventricles. The consequent shortening of diastolic ventricular fiber length results in less ventricular work. The aortic pressure and cardiac output thus decline even while atrial pressures are markedly elevated.

These data also substantiate the findings of Wilson and Meek,[12] who estimated the size of the heart by x-ray at various right atrial pressures with and without the pericardium. At similar elevated systemic venous pressures, the cardiac silhouette was larger after the pericardium had been removed. This difference in size, with and without the pericardium, increased as venous pressure was elevated.

Some previous workers state that increasing the blood volume of the acute tamponade patient is beneficial.[13] Others found it to be of slight to moderate benefit[14] and still others found it of no use whatever.[15,16] This discrepancy in views is at least partially reconciled by the data presented in Fig. 6. The question of whether or not blood transfusion will be beneficial cannot be judged solely by the patient's level of either arterial or venous pressures or both, although it is less likely to be beneficial if systemic venous pressure is markedly elevated. It may confidently be assumed that increasing the blood volume will further elevate venous pressure. From the data presented above (Fig. 6) it seems clear that only a cautious trial of transfusion will reveal in any given case whether or not it is a desirable maneuver. Should the venous pressure rise markedly without a significant elevation of arterial pressure, it is obviously unwise to continue. Should arterial pressure rise significantly with only a moderate rise in venous pressure, it is of practical value. Obviously, these considerations are of importance only when aspiration of the tamponade is either not effective or not feasible because of other factors.[17]

Further examination of Fig. 6 reveals that increasing the blood volume of the patient with severe tamponade may elevate pulmonary capillary pressure to levels that produce lung edema. Happily, however, cardiac tamponade is one of the very few circumstances in which right atrial pressure may be taken as a close approximation of left atrial pressure[18] (Figs. 1, 3, and 6). This, therefore, represents a clinical situation which is quite unusual in that the danger of pulmonary edema can be estimated by measurement of right atrial pressure.

Positive pressure breathing will appreciably increase mean extra- and intrapericardial pressures. That this factor may be of significance when tamponade is severe is evident from Fig. 3 in which there is a substantial circulatory disadvantage following the decrease of effective filling pressure by as little as 1 to 2 cm. H_2O. If artificial respiration is required, some technique should be used which elevates mean intrapleural pressure as little as possible. In this respect alternating positive-negative pressure devices are preferable to those which maintain a positive mask pressure throughout the respiratory cycle. Electrophrenic respiration[19] should be an optimal method, because it maintains the same pressure relationship as in natural breathing. Since effects similar to those

of positive pressure breathing are produced by opening the chest, it would also appear wise to perform pericardial aspiration immediately prior to thoracotomy.

Both L-epinephrine and Aramine increase the stroke work per unit of effective filling pressure.[20] On theoretical grounds this should bring about a more effective systolic ejection when the effective filling pressure (and hence diastolic fiber length) is limited by tamponade. This view is in line with the findings of Kuno[16] and administration of such substances may prove to be a valuable holding maneuver in acute cardiac tamponade.

SUMMARY AND CONCLUSIONS

Acute cardiac tamponade was studied by means of ventricular function curves, the continuous recording of systemic blood flow, and pressures in the right and left atria, the pulmonary artery, the aorta, and the pericardium. In other experiments pressures were measured in the inferior vena cava and right atrium and pulmonary veins and left atrium. The effect of increasing blood volume in the dog with varying degrees of tamponade was also observed. The following conclusions were reached.

1. A measurable pressure gradient was not found with the technique used between the vena cava and right atrium or between the pulmonary veins and left atrium either in the control or tamponade state. The hemodynamic consequences of acute cardiac tamponade, therefore, cannot be explained on the basis of inflow obstruction at the entrance of the veins into the pericardium.

2. Ventricular function curves obtained in the control state and during cardiac tamponade revealed the latter to be apparently suppressed. The degree of this apparent suppression varies with the degree of tamponade.

3. Use of the plot of ventricular work against effective filling pressure as an index of myocardial contractility made clear that the myocardium is in no way functionally impaired. Rather, the weakness of its contraction is directly attributable to the reduced effective filling pressure in diastole, the latter being due to the restraining influence of the elevated pericardial pressure.

4. An increase of blood volume produced a significant increase of aortic pressure and cardiac output in mild to moderate tamponade but produced little improvement of these values in severe tamponade. In all degrees of tamponade, infusion elevates both right and left atrial pressures and these are at much higher levels when the tamponade is severe.

5. A central venous pressure in excess of 20 cm. H_2O in the open chest dog is accompanied by a severe compromise of circulatory hemodynamics.

6. As demonstrated by the relationship between effective filling pressures and ventricular stroke work, Starling's law of the heart operates during cardiac tamponade as well as during the control state.

7. The pressure-volume relationship of the pericardium when integrated with Starling's law of the heart fully explains the acute cardiac tamponade syndrome.

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THE DIAGNOSTIC IMPORTANCE OF THE BLOOD CARBON DIOXIDE CONTENT OF PATIENTS WITH CENTRAL CYANOSIS

MARGARET M. PLATTS, M.B., M.R.C.P., AND
WILLIAM WHITAKER, M.D., M.R.C.P.

SHEFFIELD, ENGLAND

IT is sometimes difficult to distinguish clinically between cyanosis due to a congenital cardiovascular anomaly, which transfers systemic venous blood into the systemic arterial tree without passage through the pulmonary capillaries and that due to chronic lung disease, which impairs the aeration of blood in the pulmonary circulation. The observations of Campbell and others[1], Bing and others,[2] Fasciolo and others[3] and Davison and others,[4] showing low or normal arterial blood carbon dioxide levels in patients with cyanotic congenital heart disease, and of Platts,[5] who found that patients with congestive heart failure complicating chronic lung disease were anoxic and had carbon dioxide retention, suggested that the blood carbon dioxide level was of diagnostic importance in patients with central cyanosis. The present investigations were made to determine the significance of the arterial blood carbon dioxide content in such patients.

Fifty-five cyanotic patients were studied: Sixteen had congenital heart disease and two of these (1 and 3) had also congestive heart failure, twenty-three had chronic bronchitis and emphysema and sixteen had chronic bronchitis and emphysema complicated by congestive heart failure. Specimens of blood were obtained by brachial or femoral artery puncture while the patients were at rest in bed, and the oxygen and carbon dioxide contents and the oxygen capacity of each specimen were determined by the technique of Van Slyke and Neill. The percentage saturation of the blood with oxygen was calculated from the oxygen content and the oxygen capacity of the sample.

RESULTS

The oxygen saturation and the carbon dioxide content of arterial blood are shown in Tables I, II, and III and Fig. 1. The arterial blood carbon dioxide content ranges from 31 to 59 volume per cent with a mean of 40.4 volume per cent in patients with cyanotic congenital heart disease, from 38 to 63 volume per cent with a mean of 53.6 volume per cent in cyanosed patients with chronic bronchitis and emphysema, and from 62 to 71 volume per cent with a mean of 65.4 volume per cent in patients with chronic bronchitis and emphysema complicated by

From the University Department of Medicine, The Royal Hospital, and The Regional Cardiovascular Centre, The City General Hospital, Sheffield, England.

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TABLE I. ARTERIAL BLOOD OXYGEN SATURATION AND CARBON DIOXIDE CONTENT IN PATIENTS WITH CYANOTIC CONGENITAL HEART DISEASE

CASE NO.	SEX	AGE	OXYGEN SATURATION (%)	CARBON DIOXIDE CONTENT VOL. (%)	DIAGNOSIS
1*	F	22	90	33	Patent ductus arteriosus
2	F	58	81	32	Patent ductus arteriosus
3*	F	69	88	59	Atrial septal defect
4	M	25	85	40	Eisenmenger's complex
5	F	17	76	39	Eisenmenger's complex
6	F	14	81	43	Fallot's tetralogy
7	M	6	67	33	Tricuspid atresia
8	F	11	83	42	Fallot's tetralogy
9	F	24	81	53	Anomalous pulmonary veins with atrial septal defect
10	F	4	71	35	Transposition of the great vessels
11	M	7	73	39	Transposition of the great vessels
12	F	26	83	38	Eisenmenger's complex
13	F	7	88	31	Tricuspid atresia
14	M	8	77	44	Anomalous pulmonary veins with atrial septal defect
15	F	6	61	48	Transposition of the great vessels
16	M	2	50	37	Fallot's tetralogy

Range of carbon dioxide contents—31–59 vol. per cent
Mean of carbon dioxide contents—40.4 vol. per cent
***Patient in congestive heart failure**

TABLE II. ARTERIAL BLOOD OXYGEN SATURATION AND CARBON DIOXIDE CONTENT IN CYANOSED PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

CASE NO.	SEX	AGE	OXYGEN SATURATION (%)	CARBON DIOXIDE CONTENT VOL. (%)
33	M	61	81	63
34	M	66	85	57
35	F	46	90	52
36	M	51	85	38
37	M	56	69	60
38	M	54	90	50
39	M	58	86	52
40	M	51	90	61
41	M	51	89	51
42	M	32	85	60
43	M	60	89	58
44	M	63	90	44
45	M	46	81	62
46	M	56	82	45
47	M	56	81	60
48	M	63	84	49
49	M		89	49
50	M	54	89	49
51	M	52	77	56
52	M	62	82	57
53	M		88	51
54	M	48	84	55
55	M	58	79	56

Range of carbon dioxide contents—38–63 vol. per cent
Mean of carbon dioxide contents—53.6 vol. per cent

TABLE III. ARTERIAL BLOOD OXYGEN SATURATION AND CARBON DIOXIDE CONTENT IN CYANOSED PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA COMPLICATED BY CONGESTIVE HEART FAILURE

CASE NO.	SEX	AGE	OXYGEN SATURATION (%)	CARBON DIOXIDE CONTENT VOL. (%)
17	M	49	62	68
18	M	65	67	65
19	M	58	54	63
20	M	58	64	63
21	M	64	55	70
22	M	42	63	63
23	M	49	52	67
24	M	31	53	64
25	M	54	65	67
26	M	67	80	65
27	M	64	71	65
28	M	52	71	62
29	M	34	53	71
30	M	59	49	66
31	M	48	70	64
32	M	58	79	63

Range of carbon dioxide contents—62–71 vol. per cent
Mean of carbon dioxide contents—65.4 vol. per cent

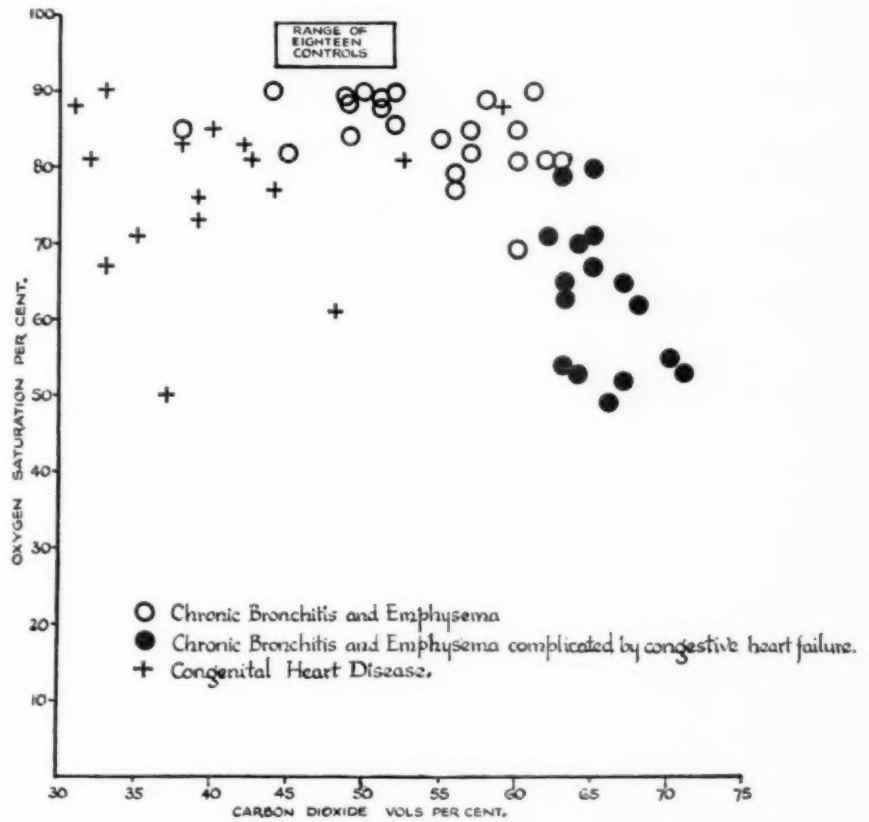
RANGE OF EIGHTEEN CONTROLS
OXYGEN SATURATION PER CENT.
CARBON DIOXIDE VOLS PER CENT.
Chronic Bronchitis and Emphysema
Chronic Bronchitis and Emphysema complicated by congestive heart failure.
Congenital Heart Disease.

Fig. 1.—Arterial blood gases in patients with central cyanosis.

congestive heart failure. The values for the controls shown in Fig. 1 were previously determined by Platts[5] who found that the carbon dioxide content of arterial blood ranged from 44 to 52 volume per cent and the oxygen saturation from 93 to 99 per cent in eighteen patients without cardiac, pulmonary, or renal disease.

DISCUSSION

The arterial blood carbon dioxide content of patients with congenital heart disease without congestive heart failure is, with one exception of 53 volume per cent, low or normal and in the majority it is less than the lower normal limit of 44 volume per cent, while that of patients with chronic bronchitis and emphysema is normal or raised, with one exception of 38 volume per cent. This suggests that an arterial blood carbon dioxide content less than the lower normal limit of 44 volume per cent indicates congenital heart disease, while one above the upper normal limit of 52 volume per cent favors chronic pulmonary disease as the cause of central cyanosis in a patient whose diagnosis is uncertain from clinical examination.

Although there were only two patients with congestive heart failure complicating congenital heart disease among those studied, the arterial blood carbon dioxide contents of these two were not so high as any found in patients with chronic bronchitis and emphysema complicated by congestive heart failure, which suggests that the blood carbon dioxide content is of diagnostic importance in cyanosed patients with congestive heart failure. A low or normal arterial blood carbon dioxide content excludes a diagnosis of congestive heart failure complicating chronic lung disease and suggests congenital heart disease as the cause of cyanosis, while conversely, an arterial blood carbon dioxide content of 62 volume per cent or over suggests that the patient is suffering from congestive heart failure complicating chronic lung disease.

The arterial blood carbon dioxide content, the carbon dioxide content of mixed venous blood, and the plasma alkali reserve are all affected by changes in the blood bicarbonate buffer system, and diagnostic criteria, similar to those given here for the arterial blood carbon dioxide content, could be established for the venous blood carbon dioxide content or for the plasma alkali reserve of patients with central cyanosis.

The present results offer no new evidence to justify a detailed discussion of the functional disturbances which produce abnormal blood carbon dioxide levels in patients with central cyanosis. The low levels associated with cyanotic congenital heart disease were attributed to chronic hyperventilation by Talbot and others,[6] while the high levels in patients with chronic lung disease were considered by Platts[5] to be due to defective aeration of blood in the pulmonary circulation, which leads to carbon dioxide retention, and a failure of the respiratory center to respond by hyperventilation to a rising blood carbon dioxide level.

SUMMARY

1. The arterial blood carbon dioxide contents were measured in fifty-five patients with central cyanosis. Sixteen had congenital heart disease and two

of these had also congestive heart failure; twenty-three had chronic bronchitis and emphysema; and sixteen had congestive heart failure complicating chronic bronchitis and emphysema.

2. The arterial blood carbon dioxide content was below normal in the majority of patients with cyanotic congenital heart disease, normal or raised in the majority of patients cyanosed from chronic bronchitis and emphysema, and invariably raised in patients with congestive heart failure complicating chronic bronchitis and emphysema.

3. The blood carbon dioxide content appears to be of diagnostic importance in patients with central cyanosis.

We wish to thank Dr. J. W. Brown, Dr. C. E. Davies, and Prof. C. H. Stuart-Harris for allowing us to investigate patients under their care.

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INTRAVENOUS PROCAINE AMIDE AS AN AID TO DIFFERENTIATE AURICULAR FLUTTER WITH BUNDLE BRANCH BLOCK FROM PAROXYSMAL VENTRICULAR TACHYCARDIA

LIONEL M. BERNSTEIN, M.D., LUKE R. PASCALE, M.D., HAROLD M. SCHOOLMAN, M.D., AND EDMUND F. FOLEY, M.D.

CHICAGO, ILL.

IT IS well known that the electrocardiographic appearance of paroxysmal ventricular tachycardia may be simulated by aberrant intraventricular conduction of rapidly transmitted impulses from paroxysmal auricular tachycardia, auricular fibrillation, auricular flutter, and paroxysmal nodal tachycardia. Since digitalis preparations are frequently used in the treatment of tachycardias of supraventricular origin and are generally considered dangerous in the treatment of ventricular tachycardias, accurate differentiation of paroxysmal ventricular tachycardia from tachycardias of supraventricular origin is very important. However, paroxysmal ventricular tachycardias frequently cannot be excluded in such cases in spite of the aid of measures to produce vagal stimulation and the scrutiny of long tracings of standard, aV, and multiple V leads. In such cases therapy must be initiated without a definitive diagnosis.

It is our belief that any paroxysmal tachycardia with prolonged QRS complexes must be considered as ventricular in origin and treated in that manner until a supraventricular origin can be conclusively demonstrated. Hence, digitalis preparations are withheld, and procaine amide (Pronestyl)* is administered intravenously. Procaine amide has the advantage of effectiveness in the treatment of paroxysmal supraventricular (auricular and nodal) tachycardias as well as of ventricular tachycardias. Its value in the recognition of auricular flutter with bundle branch block masquerading as ventricular tachycardia is the subject of this presentation. In each of five such instances changes following intravenous procaine amide administration made the correct diagnosis evident. Table I summarizes these changes during procaine amide administration.

CASE REPORTS

CASE 1.—(Fig. 1.) Regular paroxysmal tachycardia, rate 215, prolonged QRS of right bundle branch block pattern simulating ventricular tachycardia. The correct diagnosis of auricular flutter with bundle branch block became evident after the intravenous administration of 300 mg. of procaine amide by occasional dropped QRS complexes. These long R-R intervals were exactly twice the duration of the other R-R intervals, suggesting auricular flutter with a transient decrease of atrioventricular conduction from 2:1 to 4:1. Subsequently, the atrioventricular conduction ratio became predominately 4:1, the right bundle branch block changed to left bundle branch block, and auricular flutter waves became obvious.

From the Department of Medicine, Cook County Hospital, Chicago, Ill., and the Department of Medicine, University of Illinois College of Medicine, Chicago, Ill.

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*The procaine amide hydrochloride (Pronestyl) used in this study was supplied by E. R. Squibb & Sons, New York, N. Y.

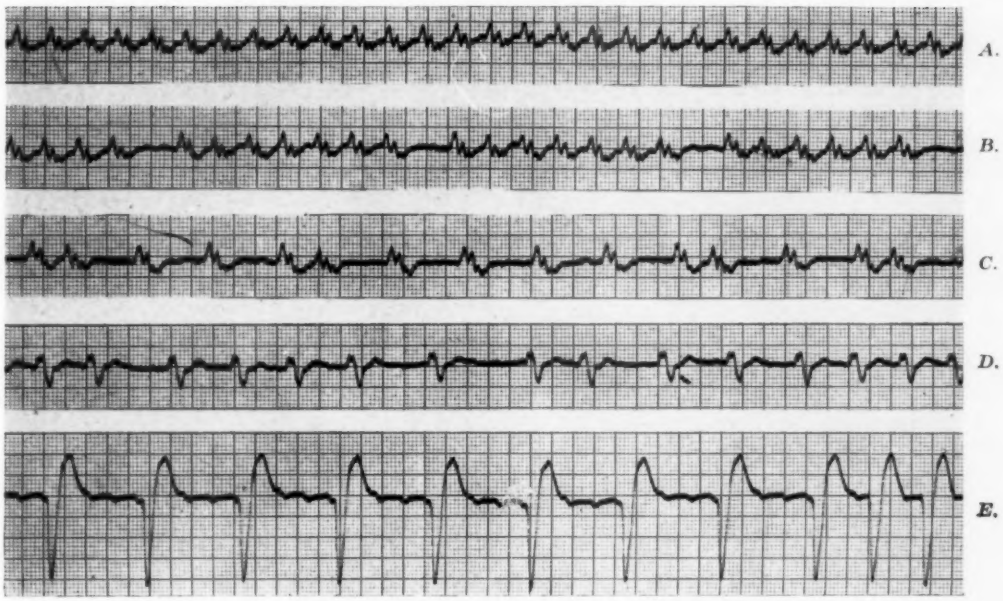

Fig. 1.—Case 1. *A*, Lead II. Auricular flutter, 2:1 atrioventricular conduction, simulating ventricular tachycardia, rate 215. *B*, Lead II after 300 mg. of procaine amide showing occasional change of atrioventricular conduction from 2:1 to 4:1. *C*, Lead II after 500 mg. showing slowing of ventricular rate due to decreased atrioventricular conduction. *D*, Lead II after 700 mg. The right bundle branch block suddenly changed to a left bundle branch block. *E*, Lead V_1 after change to left bundle branch block revealing auricular flutter waves.

Case 2.—(Fig. 2.) Irregular paroxysmal tachycardia, rate 170, prolonged QRS of left bundle branch block pattern simulating ventricular tachycardia. Intravenous administration of 600 mg. of procaine amide slowed the ventricular rate without significant change in QRS contour and caused the ventricular response to become grossly irregular. Auricular flutter waves became evident in the increased SQ segments. Such slow, grossly irregular QRS complexes of the same contour as the original rapid QRS complexes in the presence of auricular flutter indicate that the tachycardia was supraventricular in origin (auricular flutter with left bundle branch block).

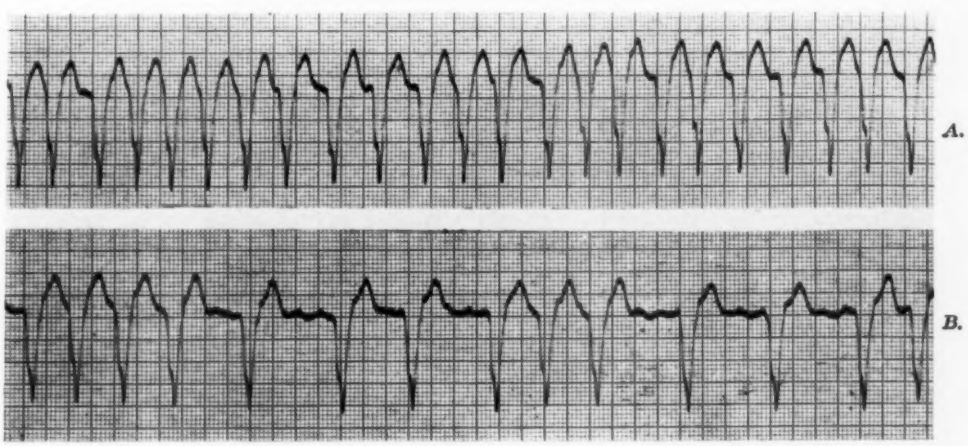

Fig. 2.—Case 2. *A*, Lead V_1. Auricular flutter, irregular due to varying atrioventricular conduction, left bundle branch block, simulating ventricular tachycardia, rate 170. *B*, Lead V_1 after 600 mg. of procaine amide showing gross irregularity of ventricular response, and the auricular flutter waves in the SQ segments.

TABLE I. PATIENTS WITH AURICULAR FLUTTER AND BUNDLE BRANCH BLOCK SIMULATING PAROXYSMAL VENTRICULAR TACHYCARDIA

CASE	SEX	AGE	CLINICAL DIAGNOSIS	POSSIBLE BUT INCORRECT ECG DIAGNOSIS	CORRECT ECG DIAGNOSIS	DOSE OF PRONESTYL TO CLARIFY DIAGNOSIS (MG.)	EFFECT OF THE PRONESTYL
1	M	72	Arteriosclerotic heart disease	P.V.T. (RBBB)*	Auricular flutter with RBBB‡ and 2:1 A-V conduction	300	Decrease in A-V conduction from 2:1 to 4:1
2	M	50	Arteriosclerotic heart disease	P.V.T. (LBBB)†	Auricular flutter with LBBB‡ and varying A-V conduction	400	Temporary increase in A-V block, revealing F waves
3	F	46	Rheumatic heart disease	P.V.T. (LBBB)	Auricular flutter with LBBB and varying A-V conduction	1,000	Temporary increase in A-V block, revealing F waves
4	F	55	Arteriosclerotic heart disease	Double tachycardia P.V.T. (LBBB) plus auricular flutter	Auricular flutter with LBBB and varying A-V conduction	700	Increase to regular 1:1 A-V conduction as auricular flutter slows
5	M	59	Acute myocardial infarction	P.V.T. (RBBB)	Auricular flutter with RBBB and 2:1 A-V conduction	300	Change in F-R intervals, so that previously hidden F waves become visible

*P.V.T. (RBBB) = Paroxysmal ventricular tachycardia, right bundle branch block type of complex, originating in left ventricular focus
†P.V.T. (LBBB) = Left bundle branch block type of complex, originating in right ventricle
‡RBBB or LBBB = Right or left bundle branch system block

CASE 3.—(Fig. 3.) Irregular paroxysmal tachycardia, rate 200, prolonged QRS of left bundle branch block pattern simulating ventricular tachycardia. The same changes occurred following administration of 1,000 mg. of procaine amide as occurred in Case 2 indicating the true diagnosis of auricular flutter with left bundle branch block.

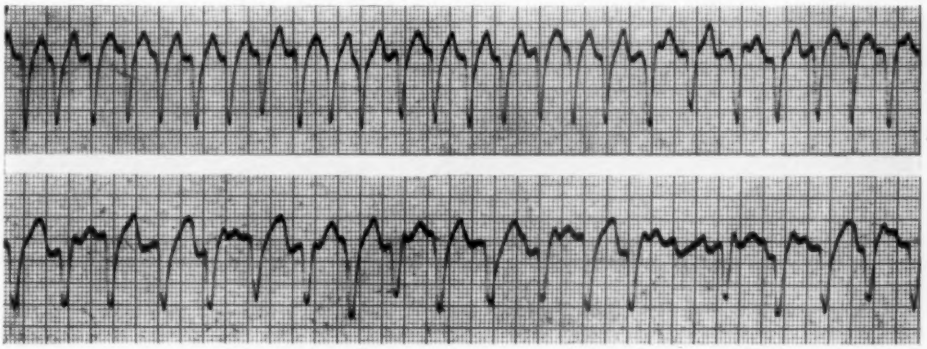

Fig. 3.—Case 3. Lead V_1. *A*, Auricular flutter, irregular due to varying atrioventricular conduction, left bundle branch block, simulating ventricular tachycardia, rate 200. *B*, After 1,000 mg. of procaine amide showing gross irregularity of ventricular response, and the auricular flutter waves in the SQ segments.

CASE 4.—(Fig. 4.) Irregular paroxysmal tachycardia, rate 130, prolonged QRS of left bundle branch block pattern simulating ventricular tachycardia; auricular flutter waves, rate 190. The differential diagnosis in this case was between auricular flutter with bundle branch block and a double tachycardia (auricular flutter plus independent paroxysmal ventricular tachycardia).

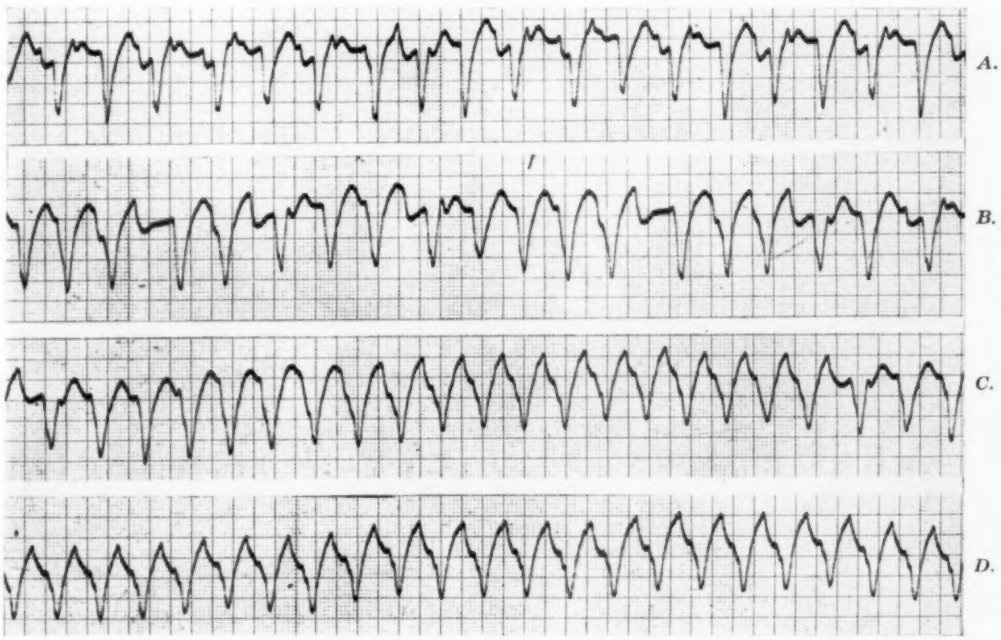

Fig. 4.—Case 4. Lead V_1. *A*, Auricular flutter, irregular atrioventricular conduction. Auricular rate 190, ventricular 130±, left bundle branch block pattern simulating ventricular tachycardia superimposed upon auricular flutter. *B*, After 300 mg. of procaine amide. *C*, After 700 mg. of procaine amide. The auricular rate has slowed, and the ventricular rate increased. *D*, After 1,000 mg. of procaine amide. The auricles have slowed to 145, the atrioventricular conduction is 1:1.

The recognition of auricular flutter waves more rapid than the ventricular rate suggests, but in no way proves, the supraventricular origin of ventricular activation. Hence, procaine amide was administered intravenously. A total dose of 1,000 mg. resulted in a gradual increase in the rate and regularity of the ventricular response. The procaine amide slowed the auricular flutter allowing increased nodal recovery time and increased atrioventricular nodal transmission. At an auricular rate of 145, the atrioventricular conduction became 1:1. These series of changes proved that the ventricles were being activated by impulses transmitted from the auricular flutter, and not by an ectopic ventricular focus.

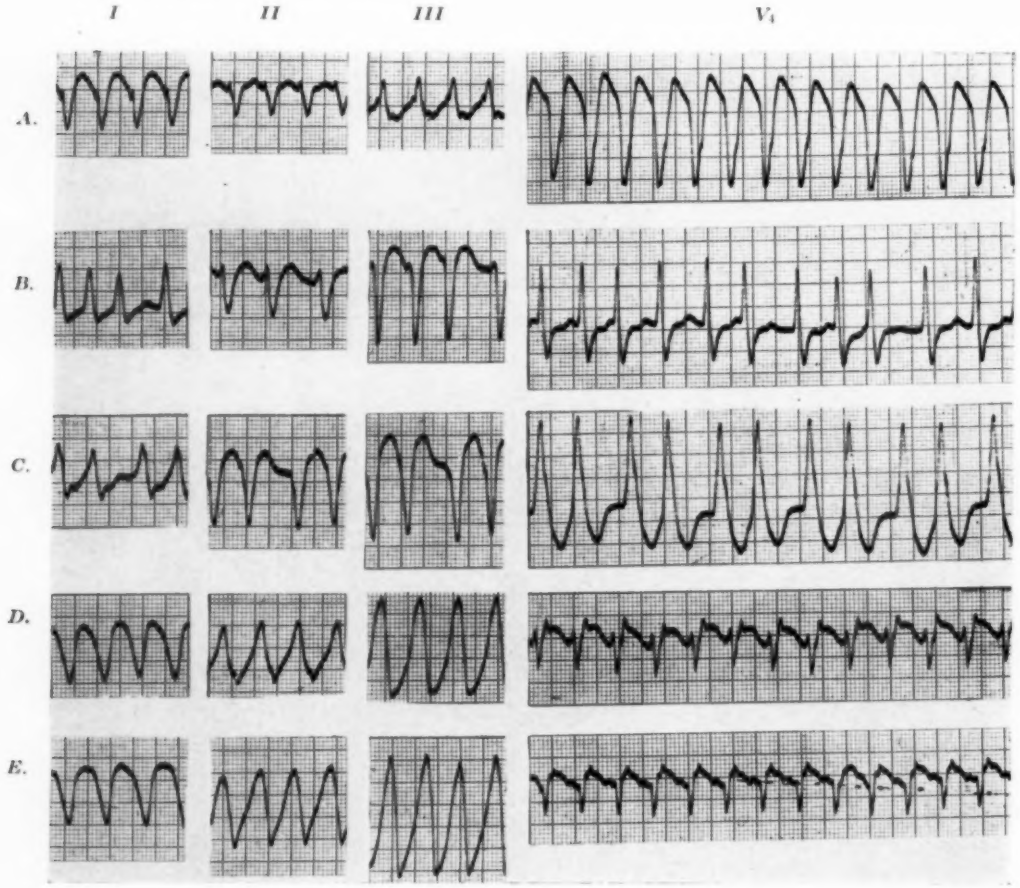

Fig. 5.—Case 5. Leads I, II, III, and V_4. *A*, Paroxysmal ventricular tachycardia, right bundle branch block type pattern. *B*, After treatment with 600 mg. of procaine amide, revealing auricular fibrillation with left bundle branch block. *C*, Bigeminal rhythm noted one day after *B*. *D*, During tracing *C*, there occurred a sudden change to a regular paroxysmal tachycardia, right bundle branch block type of pattern simulating ventricular tachycardia. *E*, After 300 mg. of procaine amide, the auricular flutter waves are discernible in Lead V_4. The atrioventricular ratio is 2:1.

CASE 5.—(Fig. 5.) Regular paroxysmal tachycardia, rate 176, prolonged QRS of right bundle branch block pattern simulating ventricular tachycardia. This patient had several episodes of tachycardias of different mechanism. The original episode was a paroxysmal ventricular tachycardia (Fig. 5,*A*) which was terminated by 600 mg. of procaine amide revealing an auricular fibrillation with left bundle branch block (Fig. 5,*B*). The following day a bigeminal rhythm (Fig. 5,*C*) was found which suddenly changed to a regular paroxysmal tachycardia (Fig. 5,*D*) resembling a ventricular tachycardia. After 300 mg. of procaine amide during a delay in administration of

the medication, auricular flutter waves became evident in Lead V_4 (Fig. 5*E*) which were not discernible before treatment. This change presumably resulted from an increase in the F-R intervals such that the F waves which had previously been obscured became obvious in the SQ segments. The diagnosis of auricular flutter with right bundle branch block with a 2:1 atrioventricular conduction ratio then became evident.

DISCUSSION

We have presented five cases of auricular flutter with bundle branch block which simulated paroxysmal ventricular tachycardia. The differentiation of these two diagnoses is important since administration of digitalis preparations is of great value for reducing quickly the rapid ventricular rate in auricular flutter with bundle branch block whereas it is considered hazardous in paroxysmal ventricular tachycardias. In each of these five cases, the diagnosis of ventricular tachycardia was originally entertained. Though in some there were hints of the true nature of the tachycardia, the diagnosis of ventricular tachycardia could not be definitely excluded in any. Therefore, these cases were initially treated as paroxysmal ventricular tachycardia with procaine amide. Following administration of procaine amide changes occurred which permitted accurate diagnosis of the mechanism in each case. These changes included (1) transient decrease of atrioventricular conduction from 2:1 to 4:1 (Fig. 1); (2) decreased atrioventricular conduction revealing flutter waves in the increased SQ segments (Figs. 1, 2, and 3); (3) a slightly irregular ventricular rhythm with 2° atrioventricular block changing to a more rapid regular rhythm as auricular slowing and 1:1 atrioventricular conduction occurred (Fig. 4); and (4) change in F-R intervals so that F waves which had been obscured became discernible between QRS complexes (Fig. 5). It is worthy of note that a marked increase in ventricular irregularity without significant alteration of the shape of the QRS complexes tends to exclude paroxysmal ventricular tachycardia. Procaine amide consistently causes a decrease in the ventricular irregularity (when originally present) along with considerable alteration of the QRS complexes as slowing of ventricular tachycardias occurs.

Thus, in each of the five patients, the diagnosis of auricular flutter with bundle branch block and the exclusion of paroxysmal ventricular tachycardia was accomplished by the changes resulting from intravenous administration of procaine amide. Then appropriate definitive digitalis therapy could be given in each case. By this means the administration of digitalis in wide QRS complex tachycardias in which a paroxysmal ventricular mechanism could not be excluded was avoided until the supraventricular origin of the tachycardia was clearly established by the electrocardiographic alterations of mechanism following intravenous procaine amide administration.

SUMMARY

In five cases of auricular flutter with bundle branch block simulating paroxysmal ventricular tachycardia the true diagnosis was established by the electrocardiographic changes following intravenously administered procaine amide.

MASSIVE T-WAVE INVERSION

THOMAS L. IPPOLITO, M.D.,* JULIUS S. BLIER, M.D., AND
THEODORE T. FOX, M.D.**

NEW YORK, N. Y.

MASSIVE T-wave inversion is an infrequent finding in electrocardiographic experience. Not a single tracing presenting this abnormality was noted among thirty thousand consecutive electrocardiograms in one of the New York hospitals (Sea View). This report of three cases with massive T-wave inversion is prompted by the fact that a common factor is believed to be present in all of them, which factor might possibly have an etiologic significance in the mechanism of this phenomenon.

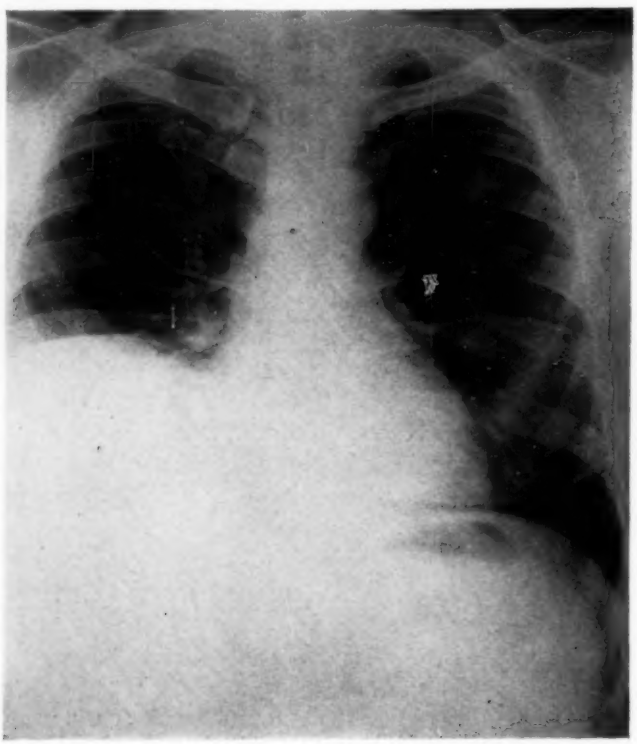

Fig. 1.—X-ray of chest of Case 1, secured in 1941.

CASE REPORTS

CASE 1. J. S., a 68-year-old male (1953) first complained of some respiratory distress in 1941. The clinical findings at that time apparently were those compatible with a diagnosis of bronchiectasis. An x-ray of the chest (Fig. 1) revealed a high and rather fixed right diaphragm, and

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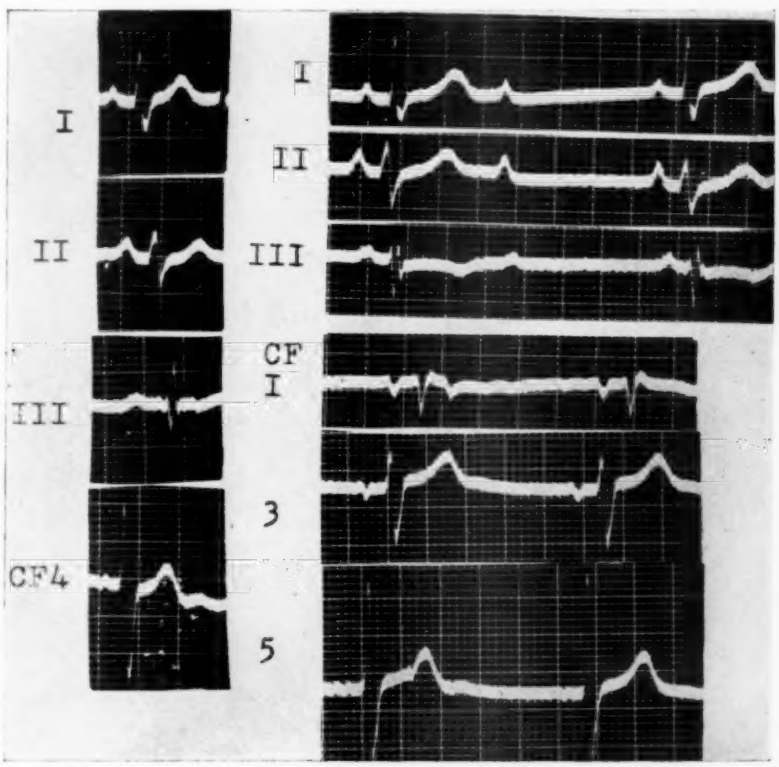
*Present address: Norwalk, Conn.
**Present address: 944 Fifth Avenue, New York 21, N. Y.

a somewhat accentuated aortic knob. An electrocardiogram secured at that time seemed to represent primarily evidence of mediastinal rotation (Fig. 2, *A*). The blood pressure reading was 110 mm. Hg systolic and 70 diastolic.

In October, 1944, the patient complained of dyspnea on effort. An electrocardiogram obtained at that time revealed a 2:1 atrioventricular block (Fig. 2, *B*). However, this phenomenon apparently was transient, as subsequent tracings presented a normal sinus rhythm with a slow rate, never exceeding 55 per minute. In September, 1950, complete A-V dissociation with a ventricular rate of thirty was first noted. The rhythm was again normal in February, 1951. Complete A-V block reappeared in July, 1952 (Fig. 3) and no transition to normal sinus rhythm was observed since then. At about this time the patient began to manifest mild syncopal attacks.



A. *B.*

Fig. 2.—*A*, Taken July 1, 1941. *B*, Oct. 14, 1944. See text.

Early in February, 1953, the patient suddenly experienced slight (?) squeezing substernal pain on exertion. He was rather vague as to the duration of the pain but was conscious of marked fatigue which followed. He was now having an increasing number of syncopal attacks. On Feb. 10, 1953, his heart rate on auscultation was 22 per minute, and his blood pressure was 180 mm. Hg systolic and 70 diastolic. On Feb. 11, 1953, the electrocardiogram for the first time was noted to present marked T-wave changes (Fig. 4). Acute myocardial damage was suspected and the patient was put to bed for a period of three weeks. On the following day the T inversion was more massive (Fig. 5). Blood studies failed to reveal significant changes in the leukocyte count, sedimentation rate, or electrolyte state. Electrocardiographic tracings secured at intervals showed gradual shallowing of the T waves but it was not until May 27, 1953, that the electrocardiogram returned to the pattern depicted on July 1, 1952. At this time the patient was back to his usual occupation complaining of only an occasional syncopal attack.

CASE 2. G. F., a 56-year-old female was known to have heart disease with conduction difficulties for at least ten years. Complete heart block (Fig. 6, *A*) was known to have been present for at least three years and this was associated with occasional episodes of loss of consciousness and convulsions. On April 5, 1951, after a period of increased activity she suddenly developed epigastric pressure with substernal radiation which lasted several hours. On physical

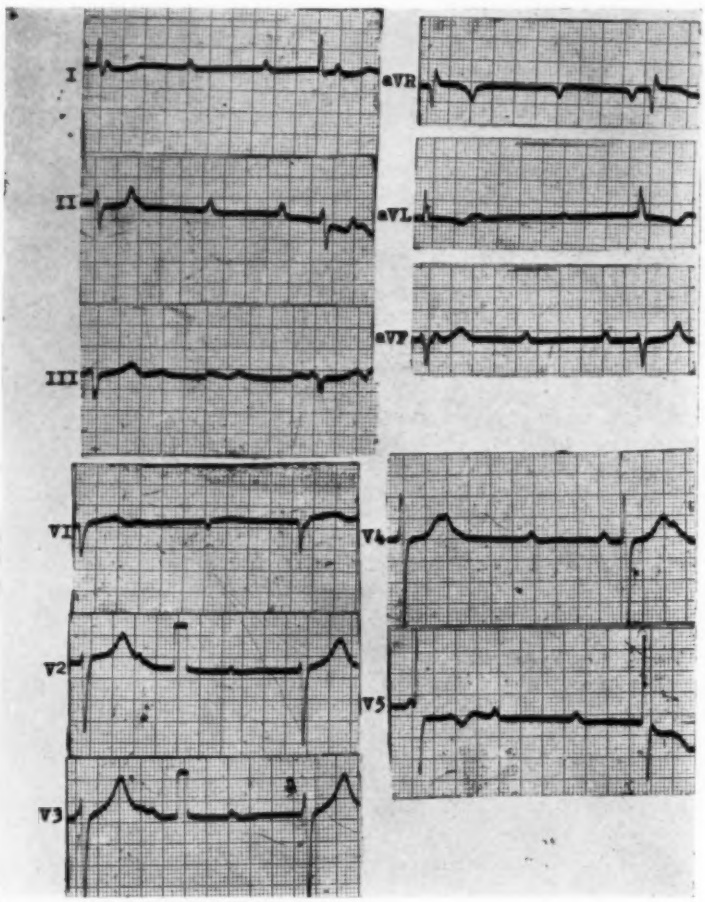


Fig. 3.—Taken July 1, 1952. See text.

examination the heart was found somewhat enlarged and the rhythm irregular. A systolic murmur was heard over the mitral area. The blood pressure was 130 mm. Hg systolic and 80 diastolic. (The usual range was 150-120 mm. Hg systolic and 60 diastolic). The electrocardiogram revealed marked T-wave inversion in Leads I, II, aV_R and aV_F and across the precordium from CF_2 to CF_6 (Fig. 6, *B*). Neither the subsequent clinical course nor the laboratory studies shed any light on the etiology of this incident. The bizarre electrocardiogram was noted to have returned to its previous pattern on April 15, 1951. The patient continued fairly well with only an occasional Stokes-Adams attack. In December, 1951, it was noted graphically that the attacks of unconsciousness were related to paroxysms of ventricular tachycardia.

On Jan. 21, 1952, following a period of rather frequent convulsive episodes the electrocardiogram again revealed the bizarre deeply inverted T waves (Fig. 6, *C*). In the same tracing frequent premature ventricular contractions and short paroxysms of ventricular tachycardia were noted. The patient's condition was critical for several days. On Feb. 6, 1952, the tracing was seen to have returned to its usual pattern.

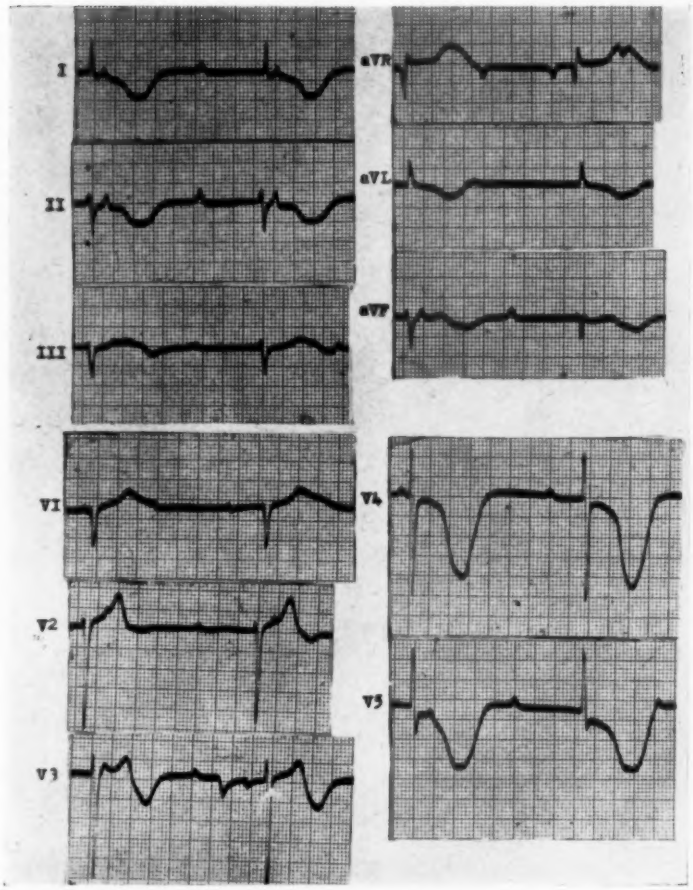


Fig. 4.—Note deep T waves and prolonged Q-T intervals. Feb. 11, 1953.

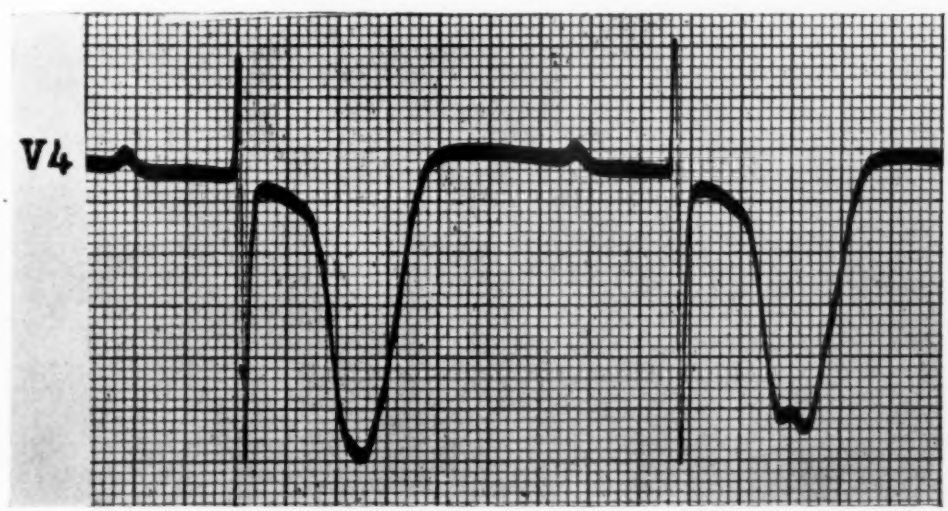


Fig. 5.—Note deep inversion of T wave and Q-T interval of 0.8 sec. Feb. 12, 1953.

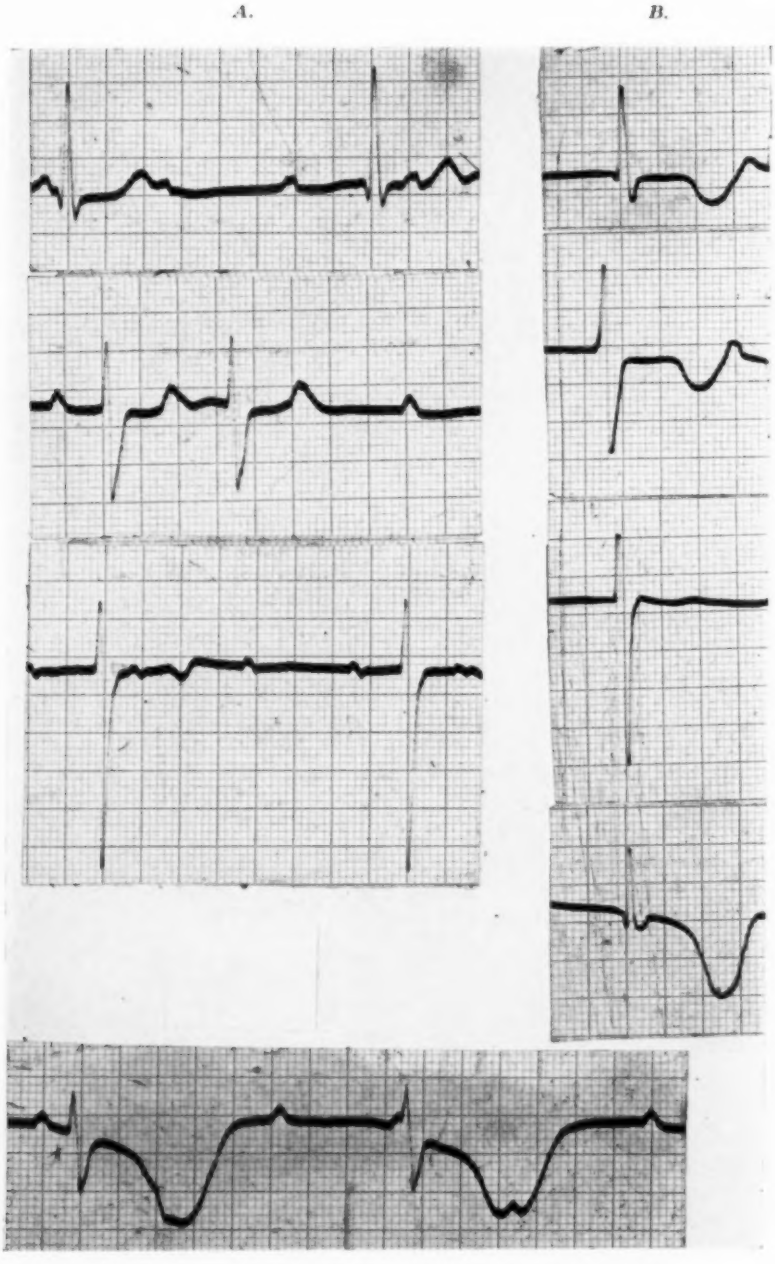


Fig. 6.—Case 2. *A*, "Usual pattern". *B*, Tracing secured on April 22, 1951, the three standard leads and CF_5. *C*, Lead II of tracing taken on Jan. 23, 1952. The tracing taken on Jan. 21, 1952, showed many premature ventricular contractions from multiple foci. Lead I resembled Lead I of 6, *B*. T_2 was 10 mm. deep and 0.36 sec. wide. T_2 was 10 mm. deep and 0.48 sec. wide. The T_{AVL} was 7 mm. tall and 0.44 sec. wide. T_{AVF} was 9 mm. deep. V_5 and V_6 presented depressed R-T and inverted T waves.

Since then the patient remained apparently well, engaging in her usual social activities. Subject to emotional outbursts, she would, however, present an occasional attack of subdiaphragmatic unrest (distention, belching, cramps, etc.) associated with palpitation and followed by a convulsive seizure. Under such circumstances, the electrocardiogram would present multiple premature contractions and/or short runs of ventricular tachycardia.

A. *B.*

Fig. 7.—Case 3. *A*, **Tracing done on Oct. 21, 1949.** *B*, **Tracing done on Sept. 29, 1953.**

CASE 3. B. E., a 42-year-old female was admitted to the cardiac clinic of the Hospital for Joint Diseases in August, 1948. She stated that prior to admission she had a heart attack. The nature of the attack could not be determined. She was practically asymptomatic on admission. In the course of the last six years, in addition to dizziness and fatigue, she would occasionally complain of some precordial discomfort. On physical examination the precordium never revealed anything of significance. The blood pressure fluctuated between 170 to 180 mm. Hg

systolic and 90 to 120 diastolic. On fluoroscopy the heart was found to be somewhat enlarged and the aorta moderately dilated. The electrocardiogram of Aug. 31, 1948, showed T-wave inversion in the three standard leads and CF_4. T_1 was seven mm. deep, T_2 nine mm., T_3 seven mm., T-CF_4 was fifteen mm. deep. The tracing of Oct. 21, 1949, is depicted in Fig. 7, *A*. The general pattern of the electrocardiogram was about the same in the several tracings secured routinely in the last six years. The depth of the T waves varied slightly and was always less marked than that recorded in Fig. 7, *A*. Fig. 7, *B* is an example of the subsequent tracings. It is to be noted that the heart rate in all of the tracings was about 50. The only tracing which showed a higher rate (60) was the one obtained on admission (August, 1948).

DISCUSSION

Massive inversion of the T wave was previously discussed by Wood and Wolferth[1] and Silverman and Goodman.[2] It should be noted that the illustrations given by these authors present the main characteristic we are reporting, namely, the slow ventricular rate. Complete heart block is apparently not essential for the massive inversion of the T wave to make its appearance. The other important factor is seemingly the existence of a coronary insult, either in the form of a myocardial infarct, as in the cases quoted, or coronary insufficiency, as observed in our cases. If these two factors are etiologically related, then the following may perhaps be stated with hesitation. The repolarization of a locally damaged heart may be delayed if the intraventricular volume is increased (prolonged diastole) and intraventricular pressure built up. It should be noted that in the cases of massive T-wave inversion the Q-T interval is affected as well as the amplitude of the T-wave (0.88 sec. in Fig. 6).

Massive T-wave inversion of the degree recorded in this report has been observed by one of us (TTF) as a result of the administration of Pronestyl.[3] It is of interest that the case in which it was observed possessed the characteristics mentioned above, namely, the slow ventricular rate and coronary insufficiency.

Sinus bradycardia and A-V block usually bring into focus the question of vagus tone. There is a possibility that the vagus plays some role in the mechanism of massive T-wave inversion. The long history of transient A-V difficulty in Case 1 and the clinically evident autonomic nervous system imbalance in Case 2 are suggestive of increased and varying vagus tone. The case illustrating the effect of Pronestyl on the T-wave[3] was one of Wolff-Parkinson-White syndrome, a most demonstrative example of vagus substance fluctuations.

SUMMARY

The subject of massive T-wave inversion is illustrated by three case reports. It seems to the authors that the prerequisites for this phenomenon are the presence of coronary insufficiency and a slow ventricular rate. The possible effect of vagus tone on the mechanism of massive T-wave inversion is briefly discussed.

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RENAL AND HYPOTENSIVE EFFECTS OF ACUTE AND CHRONIC ORAL TREATMENT WITH 1-HYDRAZINOPHTHALAZINE (APRESOLINE) IN HYPERTENSION

KENNETH VANDERKOLK, M.D., A. S. DONTAS, M.D., AND S. W. HOOBLER, M.D.

ANN ARBOR, MICH.

AMONG the commonly used antihypertensive drugs, only one, 1-Hydrazinophthalazine (Hydralazine), has been reported by various sources to produce an active dilatation of the renal vessels, when given parenterally to human subjects.[1-3] No studies on the effects of administration of single oral doses, acceptable to the patient, have been reported, and with the exception of the report of Dustan and associates,[1] and Moyer[4] no information is available concerning the effects on the kidneys of long-term therapy with this drug. Since it was hoped that continued renal vasodilatation might reverse the pathologic vasoconstriction of the kidneys in hypertensive disease, it was of particular interest to observe the effect of acute and chronic oral administration of Hydralazine on the resting renal circulation and the basal blood pressure. Such observations form the subject of this paper.

METHODS

1-Hydrazinophthalazine was administered in maximum tolerated oral doses, to seven patients with moderate "essential" hypertension but without azotemia, two of whom (V.G. and W.M.) had undergone a supradiaphragmatic splanchnicectomy, eighth vertebral ganglion to twelfth vertebral ganglion, 15 to 17 months previously. Before and at the end of an 11 to 15-weeks' period of such treatment, the renal blood flow response to a single oral dose of the drug was observed. Renal function was tested by the clearance of para-aminohippurate and inulin, according to conventional techniques. Patients were studied in the fasting state and the blood pressures and renal functions were determined during two 20-minute control periods after which the drug was given orally at the beginning of the third period. The blood and catheterized urine specimens were then collected over six additional intervals of 20 minutes each. The blood pressure for each period was recorded every 3 to 5 minutes throughout the entire procedure, and the mean value for each period was calculated by dividing the average of all systolic and diastolic readings by two. The fluid intake was constant during the test, as the patients each received intravenously 750 c.c. of fluid containing para-aminohippurate and inulin, and routinely were given 120 c.c. of water or fruit juice orally at 45-minute intervals.

From the Department of Internal Medicine, University of Michigan Medical School. This research was supported in part by grants from the Ciba Company, Summit, N. J., and by the National Heart Institute, U. S. Public Health Service.

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During clinic visits when renal blood flow determinations were not performed, the resting mean blood pressure was calculated by averaging the first two or three recumbent readings taken within 15 to 30 minutes after admission to the clinic. The blood pressure after the test dose was determined by taking the lowest mean recumbent reading during the day in the clinic, the patient remaining ambulatory in the interval between readings. The lowest blood pressure usually occurred about equally after either the first dose at 9 A.M. or the second dose at 12 noon. This system recorded the maximum possible reduction which could be ascribed to the drug.

In addition to this study, the effects of Apresoline on the foot blood flow were studied in selected patients by means of the venous occlusion plethysmographic technique of Abramson.[5]

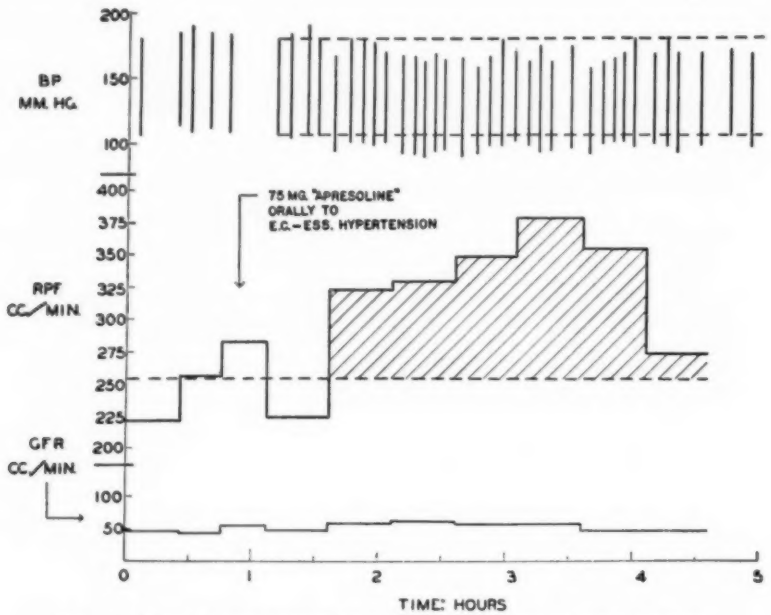

Fig. 1.—Effect of oral Apresoline on blood pressure and renal function.

RESULTS

1. *Effect on Renal Plasma Flow.*—The typical effect of a single oral dose of Hydralazine was to produce a significant increase in renal plasma flow without a significant change in glomerular filtration rate (Fig. 1). The renal vasodilator response was evident approximately 45 minutes after drug administration, was at its maximum in 2 to 2½ hours, and returned to normal levels in 3½ to 4 hours. A moderate reduction in systolic and diastolic blood pressures was also noted.

Our data in all seven cases, studied before and at the end of the period of chronic treatment with the drug, is presented in Fig. 2. The mean renal plasma flow of our patients increased from 385 ± 42.9 c.c./min.* to 523 ± 46.8 c.c./min.* following the initial administration of the drug. This difference was highly significant ($p = 0.011$).

*Mean and standard error of the mean.

At the end of the 11 to 15 weeks of treatment the same dose increased the renal plasma flow from 419 ± 43.9 c.c./min. to 422 ± 66 c.c./min., which is entirely insignificant. Resting renal plasma flow was found to be significantly higher in three of the seven patients (E.V., S.C., E.Z.) at the conclusion of the treatment period. However, the mean change of all cases,* from 385 to 419 c.c./min., was insignificant ($p = 0.35$). Crude renal resistances were found to drop significantly in every case initially, the mean reduction being 40 per cent.

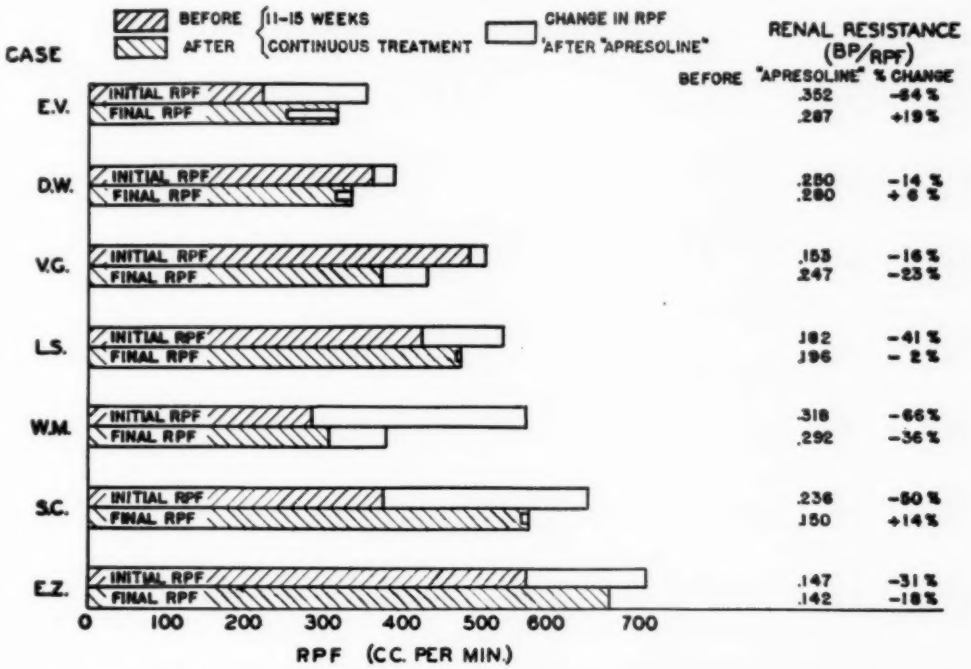

Fig. 2.—Effect of oral Apresoline on renal plasma flow in hypertension. The shaded areas represent the mean resting renal plasma flow (average of two 20-minute periods before and one 20-minute period after oral administration of the effective dose of Apresoline, as indicated in Fig. 3). The open bars indicate the mean change for the fifth to the eighth 20-minute period (third to sixth after oral Apresoline). Renal resistances are calculated by the formula (mean blood pressure divided by renal plasma flow × 1/hematocrit). It will be seen that substantial increases in renal plasma flow (average = +41 per cent) and decreases in renal resistance produced initially are less conspicuous at the conclusion of the treatment. The resting flows, however, increased slightly in three cases (EV, SC, and EZ).

In contrast, however, there was an inconstant lowering of resistance of 6 per cent when the same oral dose was given after prolonged treatment. The drug altered the filtration fraction by a mean of −21.6 per cent before and −5 per cent after the treatment interval. The changes were due in large part to the alteration in renal plasma flow. The resting filtration rate and filtration fraction were not significantly affected by the prolonged treatment.

2. Effect on Blood Pressure.—The blood pressure changes are individually plotted in Fig. 3 with the magnitude of the solid bars indicating the mean blood pressure reduction to equal doses of the drug given during the two renal blood

*Mean and standard error of the mean.

flow determinations. Open bars represent the acute blood pressure changes to varying doses given during interim visits to the clinic in the treatment period. The size of these doses is recorded on the base line. They were often reduced at these visits because patients complained of side effects from larger amounts. The height of the shaded areas on the base line indicates the daily drug intake between clinic visits. The numerals above the bars indicate the mean blood pressures before each test dose was administered. It can be readily seen that no change in the basal blood pressure occurred as a result of prolonged treatment.

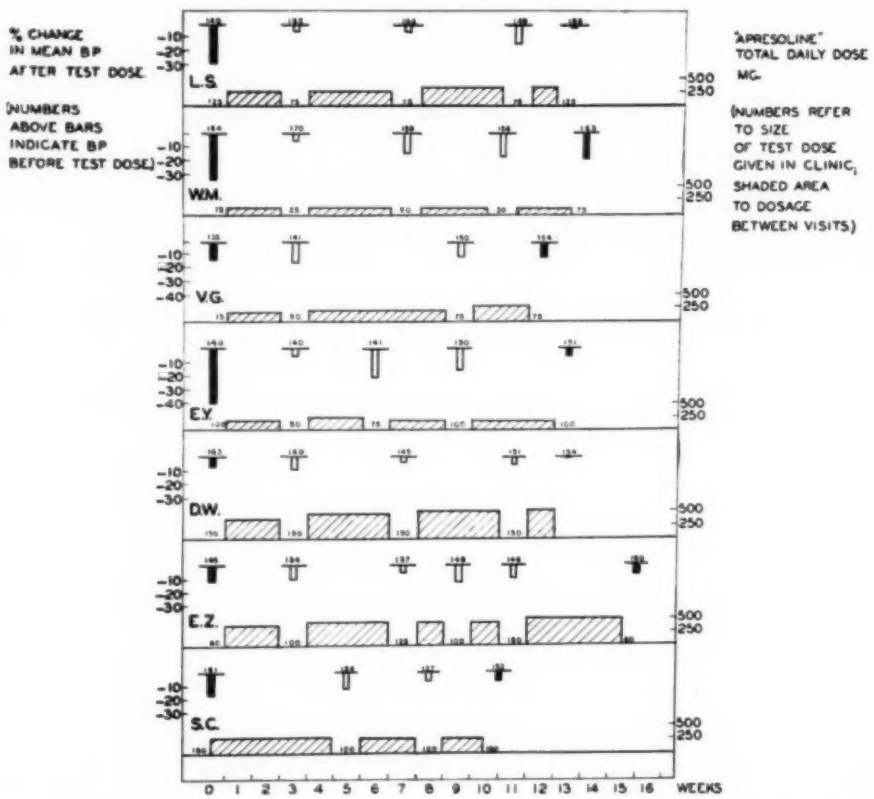

Fig. 3.—Response of recumbent blood pressure to oral Apresoline therapy. Shows changes in mean blood pressure after acute and chronic administration of Apresoline to seven hypertensive patients. Method of calculation of the resting blood pressure and the change in blood pressure after the test doses is described in the section under "Methods" and the interpretation of the figure is as described in the text in the section under "Results."

Further inspection of Fig. 3 shows that the initial test dose during the renal function test reduced the blood pressure significantly in six of the seven patients, the mean change being a −22 per cent. In contrast, the mean decrease in blood pressure during the final renal blood flow determination with the same oral dose was less prominent, representing a −8 per cent change and only two patients (W.M. and V.G.) showed a significant (i.e., greater than 10 per cent) response. This tolerance also extended to side effects, such as headache, dizziness, palpitation, nervousness and insomnia, which were much decreased on the second

administration at the end of the treatment period. Because of the development of tolerance, attempts were made to elevate the dosage taken at home, but headaches and palpitation prevented us from making substantial increases.

3. *Effect on Foot Blood Flow.*—Foot blood flow studies were done on seven patients, three of whom were also followed for their renal response to Hydralazine. In all cases a definite increase in flow was observed, occurring about 45 to 60 minutes after the ingestion of the drug and disappearing in 2 to 2½ hours (Fig. 4).

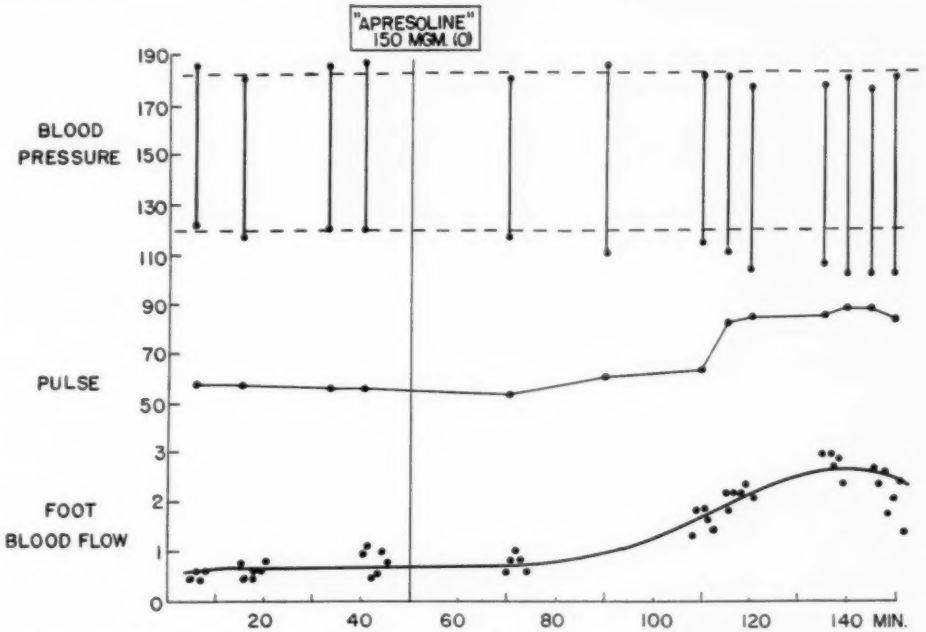

Fig. 4.—The effect of oral Apresoline on the foot blood flow as measured in the venous occlusion plethysmograph together with the changes in blood pressure and pulse rate. The definite vasodilator response to oral administration of the drug together with the widening of pulse pressure and increase of pulse rate suggests that a generalized vasodilatation is produced.

The heart rate increased considerably and there was a decrease in blood pressure, especially diastolic. The mean flow in all our patients increased from 2.72 c.c./100 c.c. of foot volume per minute to 4.4 c.c./100 c.c. of foot volume per minute. This represented a 43 per cent drop in regional resistance in this vascular bed, i.e., almost identical to that found in the renal area, in spite of the fact that the two areas are under quite unequal sympathetic tone.

DISCUSSION

The observations described above agree with those of Moyer[4] that Hydralazine is a potent renal vasodilator, but that tolerance to its renal effects is soon established. Dustan and associates[1] also noted a failure of renal vasodilatation to occur after prolonged oral treatment with the drug, but stated that in certain cases an increase in the resting renal blood flow was observed after chronic treatment. We also observed slight increases in resting renal plasma flow in three of our patients after prolonged treatment.

Observations of tolerance to the depressor effects of acute administration of Hydralazine after chronic treatment have also been reported by Moyer.[4] The report of Taylor and associates[6] does not include repeated careful studies of the acute response to oral administration of the drug before and after prolonged treatment, but it is reported that the blood pressure fell after treatment and rose when placebos were administered. Since the drug was given four times daily, it is probable that the blood pressure they recorded, particularly in the clinic, followed at least one dose of the drug and therefore does not represent changes in the "basal" level of the blood pressure. It should be emphasized that Hydralazine has a relatively transient effect and that the time since last administration of the drug is important in evaluating the blood pressure response. For the same reason it is not likely that drug administration during the day will affect blood pressure during the night unless the "basal" blood pressure level of the patient is reduced. This we have shown does not occur with the relatively small doses tolerated by our patients.

That the drug is an active generalized dilator at least in hypertensive individuals is demonstrated by our observation that peripheral blood flow in the foot is regularly increased, which parallels the observations of Wilkinson and associates,[3] and Schmid,[7] who noted increased digital temperatures following parenteral administration. Increases in splanchnic blood flow reported by Freis[8] also favor the concept that this drug is a generalized vasodilator.

The mode of action is not clearly defined, but the following bits of evidence suggest that a peripheral or central sympathetic inhibition is not involved: (a) vasodilatation in the kidney is not blocked by pretreatment with hexamethonium[4] and (b) sympathetic inhibition with tetraethylammonium results in no increases in renal blood flow and greater increases in foot blood flow than here observed.[9,10] That the drug may have a direct action on the blood vessels themselves is suggested by (a) the widespread character of the vasodilatation, (b) the effect of intra-arterial administration in increasing local blood flow in animals[11] and local skin temperatures in man,[3] and (c) absence of the hypotensive property of the drug in the spinal animals with a mean blood pressure of 60 and its reappearance if the blood pressure is raised with ephedrine.[11] It may be concluded that Hydralazine (Apresoline) is an effective generalized vasodilator in hypertension but that tolerance to its effects is soon established and that the renal hyperemia initially produced by the drug does not lead to reduction of the basal blood pressure in established hypertension.

CONCLUSIONS

1. Well-tolerated oral doses of Hydralazine produce a definite and prolonged renal vasodilatation associated with a moderate decrease in blood pressure and increase in heart rate. However, prolonged treatment diminishes these responses.

2. In three of seven patients examined after two months or more of chronic treatment, there was a slight but definite increase in resting renal plasma flow, but no change in the basal blood pressure was noted in any of the patients studied.

3. The extremital circulation shares in the vasodilator response to the drug, based on observations of foot blood flow in hypertensive patients.

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THE INFLUENCE OF A RAPID INFUSION OF GLUCOSE ON RENAL DYNAMICS AND SODIUM EXCRETION IN PATIENTS WITH ARTERIAL HYPERTENSION*

A Preliminary Report

Jan Ek, M.D., Härje Bucht, M.D., and Lars Werkö, M.D.

Stockholm, Sweden

THE renal blood flow in cases with arterial hypertension is reduced roughly proportional to the severity and duration of the hypertension. Some observers have claimed that the reduction of renal blood flow is of etiologic importance for the hypertensive state. Decrease in blood pressure in patients with hypertension may cause a further decrease of renal blood flow, but the blood pressure decrease during the pyrogenic reaction, during pregnancy or following Apresoline or hexamethonium is usually accompanied by an increase in renal blood flow of 20 to 50 per cent. During studies of the sodium excretion in different conditions it was found that rapid infusion of glucose 3 to 5 per cent in water gave an increase in renal blood flow in patients with arterial hypertension, in some cases concomitant with a marked decrease of the arterial blood pressure. This finding is detailed in the present report.

MATERIAL

Nine patients with well-established arterial hypertension were studied, three males and six females. The age ranged between 41 and 56 years. The heart size, average level of blood pressure, and eye ground findings appear in Table I.

METHODS

All patients were studied in the morning in the postabsorptive state, recumbent. One-half a liter of water was given by mouth before the procedure. A priming dosage of inulin and sodium para-aminohippurate (PAH) was given intravenously, followed by a continuous injection of inulin and PAH in physiologic saline (about 1 ml./min.). After two basal periods with this infusion, 5 per cent glucose was given with continuous injection (pulsating flow) of about 20 to 25 ml. per minute. Inulin and PAH were dissolved in this solution in a concentration that made the amount given per minute equal to what was given during the basal periods. This infusion was maintained for at least 100 minutes up to 2 hours.

From the Central Clinical Laboratory and the IVth medical service, St. Eriks Hospital, Stockholm, Sweden.

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TABLE I. HEART SIZE, DURATION OF HYPERTENSION, EYE GROUND CHANGES, AND HEIGHT OF BLOOD PRESSURE IN NINE CASES OF ARTERIAL HYPERTENSION

CASE	SEX	AGE (YR.)	BSA (SQ. M.)	HEART VOL. BSA (ML./SQ. M.)	EYE GROUND	ART. BL. PRESSURE RANGE	DURATION OF HYPERTENSION (YR.)	NPN (MG. %)	PROTEINURIA
1	M	47	1.79	470	IV	220/160–140/100	4	37	—
2	F	47	1.60	340	I	205/110–160/95	2	35	—
3	M	50	2.00	480	I	180/100–145/90	2	36	Traces
4	F	50	1.75	275	normal	185/120–150/100	10	32	—
5	F	56	2.01	415	II	250/160–160/110	15	35	Traces
6	F	44	1.67	350	III	220/140–180/115	1	39	Traces
7*	M	45	1.87	520	II-III	265/165–220/100	5	33	Traces
8*	F	41	1.67	365	II	190/120–180/70	2½	33	Traces
9	M	49	8.20	440	II	200/130–160/120	1½	34	Traces

*Operated according to Peet.

The bladder was emptied and arterial blood samples collected about ever 12 minutes. In some cases insulin was given in the glucose solution to facilitate the metabolism of the glucose and prevent glucosuria. In the later experiments only 3 per cent glucose solution was given for the same reasons. In two cases the right renal vein was catheterized with the technique of Warren and associates.[5] Blood samples were withdrawn from the renal vein simultaneously with the arterial blood samples and analyzed for PAH.

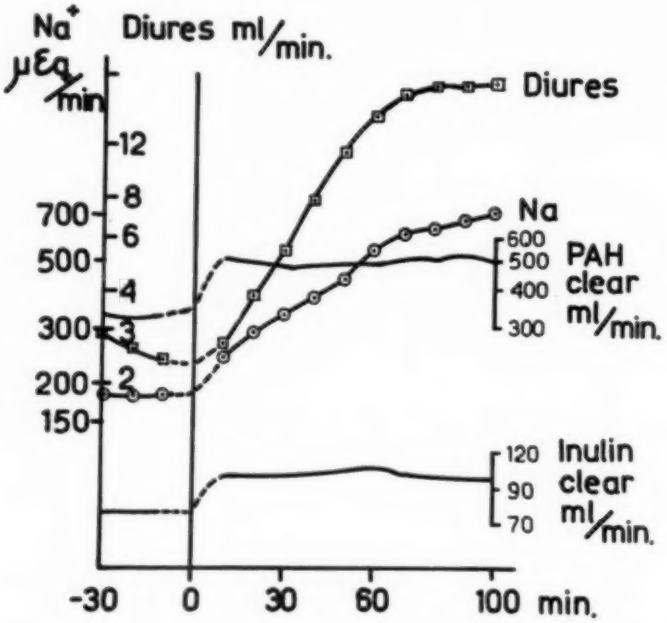

Fig. 1.—Inulin and para-aminohippurate (PAH) clearances, diuresis and sodium excretion (Na) in eight patients with arterial hypertension before and during rapid infusion of a weak solution (3 to 5 per cent) of glucose in water. The curves show the mean of the values interpolated at each even 10 minutes.

Blood samples for clearance determination were taken from an indwelling arterial needle at the start and end of each clearance period. The urinary bladder was washed twice with distilled water when the diuresis was low and rinsed with air only when the diuresis exceeded 10 ml./min.

In four cases the blood pressure was followed throughout the procedure and for a variable time afterwards.

Sodium and potassium were analyzed in the flame photometer (Weichselbaum-Varney). Inulin, PAH, endogenous creatinine, and glucose in blood and urine were analyzed according to methods and modifications related by Bucht (1951).

RESULTS

Fig. 1 shows the "mean curve" of eight patients of inulin and para-aminohippurate clearances and the excretion of water and sodium before and during

the rapid infusion of glucose. As soon as the rapid infusion starts the clearances increase and stay on the higher level during the infusion. The sodium excretion increases slowly during the infusion and shows no tendency to level off. The diuresis also increases slowly during the first 80 minutes and is then constant. The same pattern was found in all eight cases. In order to avoid tabulating all figures found during the experiments Table II contains the figures during the basal periods, the mean of the clearance values (usually 6 to 8 periods) during the rapid

TABLE II. RENAL CLEARANCES FOR ENDOGENOUS CREATININE, INULIN AND PARA-AMINOHIPPURATE, AND THE SODIUM EXCRETION BEFORE AND DURING RAPID INFUSION OF GLUCOSE SOLUTION IN EIGHT PATIENTS WITH ARTERIAL HYPERTENSION

CASE	PROCEDURE	RENAL CLEARANCE (ML./MIN.)			RENAL SODIUM EXCRETION (μ EQ./MIN.)	INFUSION RATE
		END. CREAT.	INULIN	PAH		
1	Basal	51	68	208	87	H_2O:24.4
	Glucose	92	109	558	868	G: 1.22
						I: 0
2	Basal	55	82	418	77	H_2O: 28.2
	Glucose	72	117	592	1162	G: 1.41
						I: 0
3	Basal	129	122	581	45	H_2O: 31.1
	Glucose	148	151	822	822	G: 0.84
						I: 0.61
4	Basal	83	69	413	176	H_2O: 23.4
	Glucose	98	92	522	738	G: 0.63
						I: 0
5	Basal	59	67	302	266	H_2O: 26.2
	Glucose	69	84	389	337	G: 0.71
						I: 0
6	Basal	54	51	162	209	H_2O: 23.8
	Glucose	67	62	266	747	G: 1.19
						I: 0
7	Basal	69	64	235	317	H_2O: 24.8
	Glucose	90	96	405	508	G: 1.24
						I: 0.49
8	Basal	70	72	326	274	H_2O: 28.5
	Glucose	82	90	440	542	G: 1.43
						I: 0.34
M 1-8	Basal	71	74	331	181	
	Glucose	90	100	499	716	
Diff.		18.5 $\pm$ 3.5 t = 5.3	25.8 $\pm$ 3.6 t = 7.2	169 $\pm$ 31.5 t = 5.4	534 $\pm$ 122 t = 4.4	

H_2O = water ml./min.
G = glucose g./min.
I = insulin units/min.

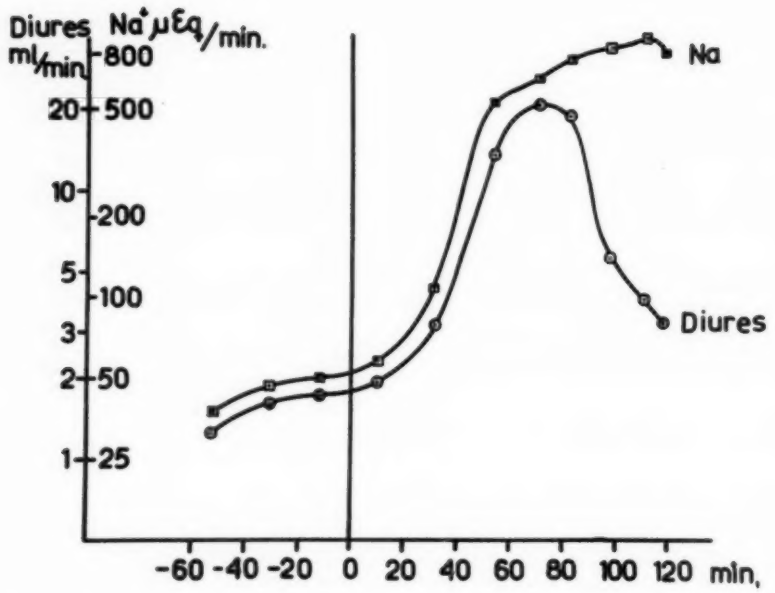

Fig. 2.—The diuresis and sodium excretion (Na) in one case of hypertension before and during rapid infusion (22 ml./min.) of 5 per cent glucose in water.

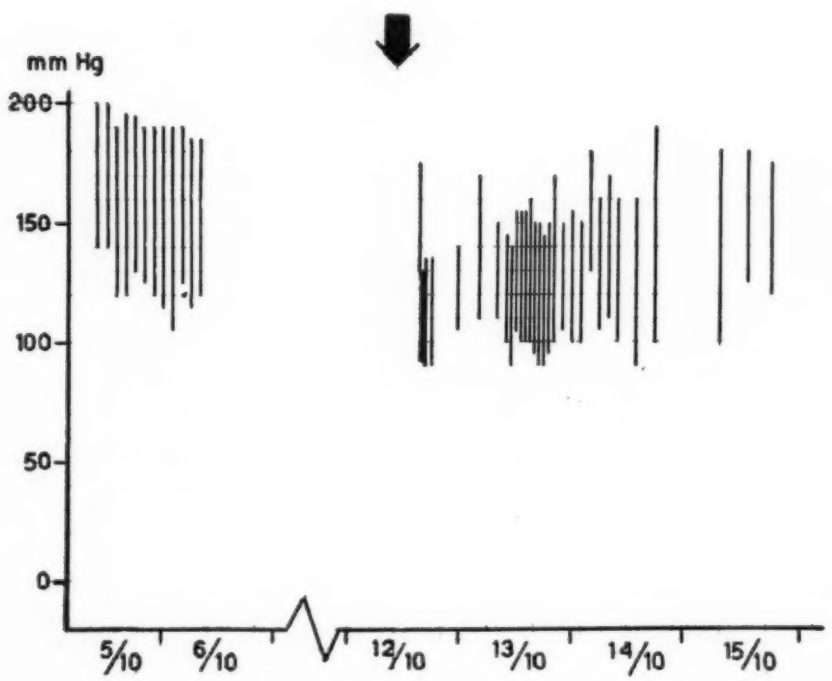

Fig. 3.—The blood pressure before and after rapid infusion of 5 per cent glucose in water in Case 5.

infusion, and the value for sodium excretion during the period 100 minutes after the start of the infusion. In all cases the clearances increased, the PAH clearance toward but usually not to normal values. The sodium excretion regularly increased up to several hundred per cent.

The sodium excretion and diuresis are not parallel. This is shown in Fig. 2. In this case (No. 3) the diuresis first increased and then fell though the rapid infusion continued. The sodium excretion on the contrary continued to increase.

The increase in PAH clearance reflects a greater increase in renal blood flow. In two cases where renal venous blood was obtained the renal extraction decreased from 90 to 78 per cent and from 92 to 80 per cent.

In some cases the blood pressure decreased after the rapid glucose infusion. Fig. 3 shows the blood pressure values in Case 5, determined every other hour during a few days before and immediately after the infusion.

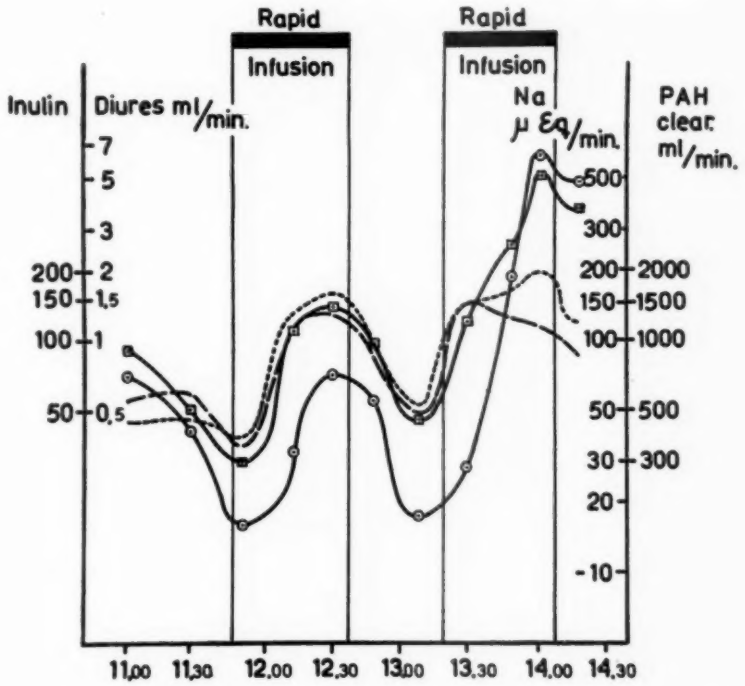

Fig. 4.—Inulin and para-aminohippurate clearances, diuresis, and sodium excretion during two periods of rapid infusion of 3 per cent glucose in water. During the period before and between the rapid infusion periods the patient received slow infusion of physiologic saline (Case 9).

Sodium (0–0). Diuresis (□—□). PAH clearance (. . . . .). Inulin clearance (— —).

Fig. 4 demonstrates the values for clearances and sodium and water excretion in a case where the rapid infusion is interrupted for 30 minutes, during which a slow infusion is given. The clearance values increase and decrease suddenly when the rapid infusion starts and stops.

COMMENTS

When sodium para-aminohippurate and glucose are mixed a compound develops that has lower excretion through the kidneys than PAH. The result is lower PAH clearance and decreasing renal extraction.[1] The result in our two cases where renal venous blood was obtained confirms the decreased renal extraction. The renal blood flow thus increases more than the increase in clearance for PAH shown in Table II and Fig. 1.

The amount of sodium excreted in 100 minutes after the start of the rapid infusion is negatively correlated to the basal values for sodium excretion ($r = -0.83$). That is, the lower the basal values, the higher is the value after 100 minutes of infusion.

There is no convincing correlation between the recorded changes in filtration rate or renal blood flow to the increase in sodium or water excretion. This together with the totally different times after the start of the rapid infusion that the clearances and the sodium excretion change (Fig. 1) shows that the excretion of sodium can be altered independently of the filtration rate.

The reason for the changes found in the present study is not clear. Some statements can, however, be made:

They are not caused by osmotic diuresis. The results are the same whether we use 3 per cent glucose plus insulin to keep the blood sugar at 120 mg. per cent or 5 per cent glucose without insulin giving a blood sugar between 300 and 400 mg. per cent.

They are not due to pyrogens in the inulin.[2] The increase in clearances always comes immediately with the start of the rapid infusion irrespective of the time lag since inulin was given. This time has varied considerably. Only one of the cases had any febrile reaction. Work in progress further shows a different result regarding the sodium excretion during a pyrogenous reaction compared to the present study.

There is no evidence that a substance giving the results is synthetized in the PAH-inulin glucose mixture; the results of preliminary studies are the same whether inulin is not used or if PAH is substituted with Diodrast.

The rapid increase in renal blood flow after the start of the rapid infusion may be mediated through some reflex pathway.

In the cases where the blood flow through the kidneys increased most the arterial blood pressure decreased to normal values and remained there for at least 24 hours. This observation is similar to the findings during and after the pyrogenic reaction[2,4] and again emphasizes the functional nature of the renal changes especially in early cases of arterial hypertension.

SUMMARY

1. The renal clearances for inulin, endogenous creatinine, sodium para-aminohippurate and sodium excretion were determined in nine cases of arterial hypertension before and during a rapid infusion of 5 or 3 per cent glucose in water.

2. The low basal clearances immediately increased to normal or near normal values in all cases when the rapid infusion was started.

3. The excretion of sodium and water slowly increased during the experiment. The diuresis increased approximately to a rate about 50 per cent of the infusion rate. The sodium excretion increased up to several hundred per cent. There was a statistically significant negative correlation between the basal value for sodium excretion and the maximal value reached during the infusion.

4. The glomerular filtration rate and sodium excretion varied independently of each other.

5. In four cases where the blood pressure was followed during and after the study, it decreased markedly for several days.

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INTRAVENOUS PROCAINE AMIDE IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

LUKE R. PASCALE, M.D., LIONEL M. BERNSTEIN, M.D., HAROLD M. SCHOOLMAN, M.D., AND EDMUND F. FOLEY, M.D.

CHICAGO, ILL.

INTRODUCTION

PROCAINE amide (Pronestyl)* has recently been shown to be a potent and highly effective substance for the suppression of ventricular tachycardia. The action of Pronestyl on supraventricular tachycardias was first considered to be of limited therapeutic value. Subsequently, however, Berry and associates[1] used procaine amide successfully to establish sinus rhythm in eighteen of twenty-two episodes of supraventricular tachycardia. It would seem timely to evaluate in which types of paroxysmal tachycardia procaine amide is effective.

In 1950, we began a study of the effectiveness of intravenously administered procaine amide on patients in the Cook County Hospital found to have a rapid heart action. A total of thirty-three patients with forty episodes were treated. This included paroxysmal ventricular tachycardias, paroxysmal supraventricular tachycardias (auricular or nodal), and auricular flutter. We have found reported 170 other instances of these arrhythmias treated with procaine amide administered intravenously.[1-18]

METHOD

When a patient with rapid heart action was discovered, our team was notified for the purpose of evaluation and treatment. An electrocardiogram was taken immediately. When no auricular activity was observed in the routine standard, unipolar limb, and chest lead positions, the anterior chest wall was searched for a lead position which would most clearly demonstrate auricular activity. Usually this was found near the V_1 position. This position was used for making the continuous electrocardiographic observations. Procaine amide was administered exclusively by the intravenous route. The drug was administered at a maximal rate of 100 mg. per minute, but no arbitrary limit was set for the total dosage. The limitation of total dose was determined by the electrocardiographic and clinical response of the patients. The electrocardiogram was under continuous observation, and tracings were recorded after the administration of each 100 mg. of procaine amide.

From the Department of Medicine, Cook County Hospital, Chicago, Ill., and the Department of Medicine, University of Illinois College of Medicine, Chicago, Ill.

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None of these patients responded to pressure on the carotid sinuses or eyes. In five cases, *l*-norepinephrine intravenous infusion was used to combat hypotension.[19] In ten episodes, acetylcholine was administered intravenously prior to procaine amide. These and other studies of the effect of acetylcholine on paroxysmal tachycardias are in preparation.

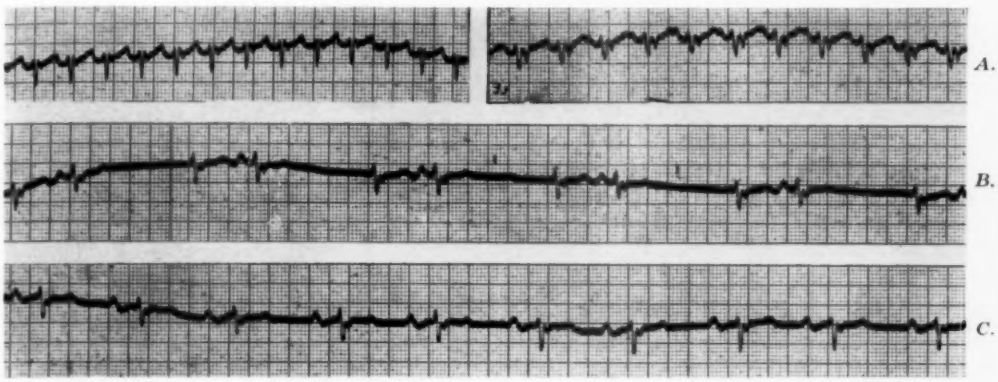

Fig. 1.—Case 4. Lead V_1. *A*, Paroxysmal auricular tachycardia before treatment, rate 180; after 700 mg. of procaine amide, rate 140. *B*, After 1,000 mg. of procaine amide, the auricular tachycardia is terminated. There is a 2:1 sinoauricular block with nodal escapes. *C*, Two minutes after *B* normal sinus rhythm is present.

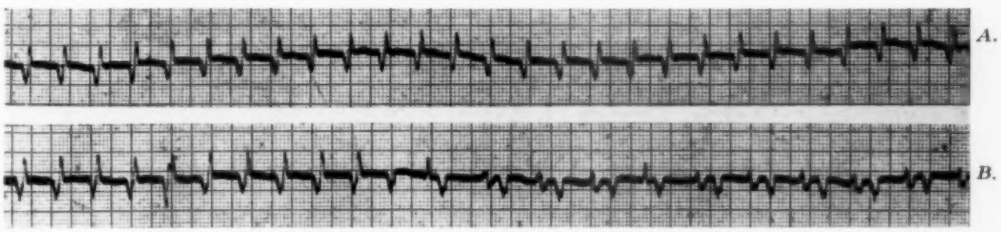

Fig. 2.—Case 9. Lead V_1. *A*, Paroxysmal nodal tachycardia, before treatment, rate 170. *B*, After 300 mg. of procaine amide the nodal tachycardia is terminated and sinus rhythm restored. The peaked R wave in *A* is now seen to be a retrograde P wave.

RESULTS

Supraventricular Tachycardia.—The treatment of thirteen episodes of supraventricular tachycardia is summarized in Table I. The conversion of paroxysmal auricular tachycardia to sinus rhythm occurred in three patients with double tachycardia, (Cases 1a, 2a, 3a reported previously)[20] after receiving doses of 500, 200, and 100 mg., respectively. The fourth instance, Case 4, reverted to the sinoauricular pacemaker with 1,000 mg. of procaine amide. The foci of origin of the supraventricular tachycardia could not be determined in Cases 5 and 6. Sinus mechanism was re-established after receiving 200 mg. and 800 mg. of the drug, respectively. In all six of these patients, the correction from paroxysmal supraventricular tachycardia to sinus rhythm was accomplished without side effects. An example of a paroxysmal auricular tachycardia is shown in Fig. 1 (Case 4).

TABLE I. EFFECT OF INTRAVENOUSLY ADMINISTERED PROCAINE AMIDE ON PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS

CASE	SEX	AGE	CLINICAL DIAGNOSIS	EKG DIAGNOSIS	AURICULAR RATE							TOTAL DOSE (Mg.)	REMARKS
					CONTROL	AFTER PROCAINE AMIDE 200	500	1,000	1,500	2,000	2,500		
1_{1a}	M	50	Old myocardial infarct	Double tachycardia P.A.T. plus P.V.T.	142	130	Converts to S.R., 68					500	P.V.T. converted to S.R. on 1,400 mg. (Table III)
2a	M	65	Acute myocardial infarct	Double tachycardia P.A.T. plus P.V.T.	150	Converts to S.R., 80						200	P.V.T. converted to N.T. on 1,500 mg.; patient died 3 days later (Table III)
3a	F	80	Arteriosclerotic heart disease	Double tachycardia P.A.T. plus P.N.T.	200	Converts to S.R., 75						100	See 3b. Postmortem exam. revealed diffuse myocardial fibrosis
4	M	61	Arteriosclerotic heart disease	P.A.T.	180	165	145	130	Converts to S.R., 65			1,000	Transient 2:1 S-A block upon conversion; failure on 90 mg. ACH., previously
					VENTRICULAR RATE								
					CONTROL	AFTER PROCAINE AMIDE 200	500	1,000	1,500	2,000	2,500		
5	M	21	Normal heart	P.S.T.	265	260	Converts to S.T., 110					200	
6	M	57	Arteriosclerotic heart disease, decompensated	P.S.T.	210	200	188	Converts to S.T. 130				800	Died from refractory cardiac decompensation 3 days after treatment

7	F	45	Normal heart	P.N.T. with 1:1 retrograde conduction	175	170	Converts to S.R., 85						200	
8	M	56	Arteriosclerotic heart disease	P.N.T. with 1:1 retrograde conduction	180	170	Converts to S.R., 90						200	Previously failed to convert with 100 mg. ACH
9	F	39	Rheumatic heart disease, decompensated	P.N.T. with 1:1 retrograde conduction	170	170	Converts to S.T., 115						300	
10	M	44	Hypertensive heart disease	P.N.T. with 1:1 retrograde conduction	170	160	160	155	Converts to S.R., 100				1,400	Hypotension treated with *l*-norepinephrine
3b	F	80	Arteriosclerotic heart disease	Double tachycardia P.A.T. plus P.N.T.	125	120	115	110	110				1,600	P.N.T., not converted; patient died 3 days later (See 3a)
11	F	46	Cirrhosis and cholemia	P.N.T., with 1:1 retrograde conduction	170	160	152	150	147	143	128		2,900	P.N.T. not converted; momentary conversion with 60 mg. ACH; patient died 3 days later
12	M	48	Normal heart	P.N.T. with 1:1 retrograde conduction	175	165	160	152	142				1,700	Failure due to hypotension, *l*-norepinephrine subsequently used; converted with 100 mg. ACH.

P.A.T.: Paroxysmal auricular tachycardia.
P.N.T.: Paroxysmal nodal tachycardia.
N.T.: Nodal tachycardia.
P.S.T.: Paroxysmal supraventricular tachycardia.
P.V.T.: Paroxysmal ventricular tachycardia.
S.R.: Sinus rhythm.
S.T.: Sinus tachycardia.
ACH: Acetylcholine, administered intravenously.

TABLE II. EFFECT OF INTRAVENOUSLY ADMINISTERED PROCAINE AMIDE ON AURICULAR FLUTTER

CASE	SEX	AGE	CLINICAL DIAGNOSIS	EKG DIAGNOSIS	AURICULAR AND VENTRICULAR RATES (A/V)									TOTAL DOSE (MG.)	TIME FOR ADM'N (MIN.)
					CONTROL		AFTER PROCAINE AMIDE (MG.)								
							200	500	1,000	1,500	2,000	2,500	3,000		
13	F	70	Hypertensive heart disease	Auricular flutter, varying A-V conduction	A / V	300 / 120±	290 / 140±	280 / 140	280 / 140	250 / 125	250 / 120±	250 / 125	240 / 120	3,000	90
14	F	45	Rheumatic heart disease	Auricular flutter, varying A-V conduction	A / V	450 / 110±	420 / 100±	330 / 110±	300 / 130±	280 / 110±				1,500	40
15	M	65	Arteriosclerotic heart disease	Auricular flutter, 2:1 A-V conduction	A / V	300 / 150	280 / 140	250 / 125	240 / 130±	240 / 130±	230 / 160±			2,000	80
16	F	45	Hypertensive heart disease	Auricular flutter, 2:1 A-V conduction	A / V	260 / 130	250 / 125	230 / 115	205 / 205					700	10
17	F	25	Rheumatic heart disease	Auricular flutter, varying A-V conduction	A / V	450 / 120±	400 / 120±	300 / 120±	280 / 120±					1,000	15
18a	F	56	Rheumatic heart disease	Auricular flutter, varying A-V conduction	A / V	270 / 70±	220 / 70±	210 / 80±	155 / 80±	130 / 80±	135 / 70±	140 / 70±	115 / 110±	3,000	110
18b					A / V	200 / 80±	195 / 65	155 / 65±	140 / 70	130 / 65				1,500	20
19	M	58	Chronic alcoholism, cirrhosis	Auricular flutter, 2:1 A-V conduction	A / V	300 / 150	290 / 145	260 / 140±	240* / 160±	220 / 130±				1,600	27

*Aberrant intraventricular conduction (see Case Report).

Of seven patients with nodal tachycardia, conversion was successful in four. Cases 7 and 8 responded to 200 mg. of procaine amide, Case 9 required a dose of 300 mg., and Case 10 needed 1,400 mg. Case 10 developed hypotension after 800 mg. had been administered. After restoration of a satisfactory blood pressure by the intravenous infusion of *l*-norepinephrine solution, an additional 600 mg. of procaine amide produced the sinus rhythm. The termination of the paroxysmal nodal tachycardia in Case 9 is shown in Fig. 2.

In three patients procaine amide therapy failed because of significant hypotension (Cases 3b, 11, and 12). Cases 3b and 11 received, respectively, doses of 1,600 and 2,900 mg. No *l*-norepinephrine was given. In Case 12, hypotension which occurred after 1,700 mg. of procaine amide was successfully corrected with *l*-norepinephrine. However, further administration of procaine amide did not seem advisable.

Auricular Flutter.—Seven patients with auricular flutter (Cases 13 to 19, Table II) were treated with 700 to 3,000 mg. of procaine amide. The auricular and ventricular rates during treatment are presented in Table II. Five of these patients developed hypotension. Because of failure of treatment in all cases and the occurrence of one death (Case Report, Appendix) no additional patients with auricular flutter with normal ventricular conduction were treated.

Ventricular Tachycardia.—A total of twenty instances of paroxysmal ventricular tachycardia were observed in sixteen patients (Cases 20 to 33, Table III). These were of two varieties: the persistent type, observed seventeen times, and the intermittent type, three times. The intermittent paroxysms (Cases 20, 21, 22) required 200 to 400 mg. to suppress the ventricular ectopic activity. Auricular flutter was also present in two of these three cases.

Seventeen episodes of persistent ventricular tachycardia in thirteen patients were treated with 300 to 2,500 mg. of procaine amide. The conversion of these tachycardias was to sinus mechanism in twelve (Cases 1, 24, 25, 26, 27, 31, 32, 33), nodal rhythm in three (Cases 2_b, 29, 30), auricular flutter in one (Case 23) and auricular fibrillation in one (Case 28). In eleven episodes (doses 300 mg. to 1,700 mg.) the conversion occurred without significant hypotension. In two episodes (Cases 2b, 31) procaine amide was given in spite of uncorrected hypotension (systolic pressure under 80 mm. Hg). *l*-Norepinephrine was administered to elevate the hypotension caused by procaine amide therapy in Case 24_3 (110/70 to 80/65 mm. Hg), Case 25 (80/70 to 50/? mm. Hg) and Case 32 (100/80 to 80/10 mm. Hg) and to elevate an initial hypotension in Case 29 (no pressure discernible). The typical termination of a paroxysmal ventricular tachycardia is shown in Fig. 3 (Case 1_2).

DISCUSSION

The object of treatment in paroxysmal tachycardia is termination of the abnormal rapid heart action as safely and as quickly as possible. The danger of paroxysmal tachycardia lies in the shortened diastolic period which diminishes cardiac output and coronary artery flow. Such effects may be tolerated for long periods of time by people with good cardiac reserve, but may lead quickly

TABLE III. EFFECT OF INTRAVENOUSLY ADMINISTERED PROCAINE AMIDE ON PAROXYSMAL VENTRICULAR TACHYCARDIA

CASE	SEX	AGE	CLINICAL DIAGNOSIS	EKG DIAGNOSIS	VENTRICULAR RATE						TOTAL DOSE (MG.)	REMARKS
					CONTROL	AFTER PROCAINE AMIDE (MG.) 200 : 500 : 1,000: 1,500: 2,000: 2,500						
20	M	65	Acute myocardial infarct	Intermittent P.V.T. (RBBB)	Frequent runs, suppressed by 400 mg.						400	
21	M	70	Arteriosclerotic heart disease	Intermittent P.V.T. (RBBB) plus auricular flutter with LBBB	Frequent runs, suppressed by 200 mg.						200	Patient died 2 days later
22	M	48	Arteriosclerotic heart disease	Intermittent P.V.T. (RBBB) plus auricular flutter	Frequent runs, suppressed by 300 mg.						300	
1_{1b}	M	50	Old myocardial infarct	Double tachycardia, P.V.T. (RBBB) plus P.A.T.	170	155	140	120	112, Converts to S.R., 80		1,400	
1_2				P.V.T. (RBBB) plus sinus P waves	155	150	135	110, Converts to S.R., 80			900	
1_3				P.V.T. (RBBB) with 1:1 retrograde conduction	160	155	140	110, Converts to S.T., 105			1,000	
2_b	M	65	Acute myocardial infarct	P.V.T. (LBBB) with P.A.T.	135	115*	115	110, Converts to nodal rhythm at rate 90			1,500	Converted to N.T. after 1,500 mg., patient died 3 days later
23	M	80	Hypertensive-arteriosclerotic heart disease, decompensated	P.V.T. (RBBB), no P waves discerned	175	170	146, Converts to auricular flutter with varying A-V conduction				400	Patient died 2 days later
24_1	M	36	No evidence of heart disease	P.V.T. (RBBB), auricular mechanism undetermined	232	220	210	160, Converts to S.R., 95			1,000	
24_2				P.V.T. (RBBB), with 2° retrograde conduction block	170	165, Converts to S. R., 75					350	
24_3				P.V.T. (RBBB) with 2:1 retrograde conduction block	214	200	168	152	150, Converts to S.R., 92		1,800	Hypotension treated with *l*-norepinephrine

25	M	74	Recent myocardial infarct	P.V.T. (LBBB) with 2° retrograde conduction block	190 142 128	175 150 135 130 120 115 110 127 127 126 115, Converts to S.R., 105	1,000 1,200 1,800	Stopped because of hypotension; Again stopped because of hypotension; *l*-norepinephrine begun, conversion effected, patient died 2 days later
26	M	55	Arteriosclerotic heart disease	P.V.T. (RBBB), with sinus P waves	200	190 160, Converts to S.R., 90	800	
27	M	60	Arteriosclerotic heart disease	P.V.T. (RBBB), no P waves discerned	175	160 155, Converts to S.R., 88	800	
28	M	59	Old and recent myocardial infarcts	P.V.T. (RBBB) P waves not discerned	200	185, Converts to auricular fibrillation with LBBB, ventricular rate 140	300	Subsequently developed auricular flutter with RBBB, patient died 10 days later
29	F	55	Hypertensive heart disease, and acute myocardial infarct	P.V.T. (RBBB), with sinus P waves	210	190 160 130, Converts to N.T., 130	1,400	*l*-norepinephrine for initial hypotension, subsequently developed chaotic rhythm, patient died 3 days later
30	M	45	Acute myocardial infarct	P.V.T. (RBBB) 1:1 conduction	158	155 150 Converts to N.T., 130	400	Subsequently converted to S.R. on oral procaine amide
31	M	50	Acute myocardial infarct	P.V.T. (RBBB), with sinus P waves	170	165 145 135 135 126 108 Converts to S.R., 65	2,500	Died 10 days later after extension of infarction
32	F	46	Acute myocardial infarct	P.V.T. (RBBB), P waves not discerned	210	194 152 138, Converts to S.R. with LBBB pattern, 78	1,000	Hypotension treated with *l*-norepinephrine
33	F	57	Acute myocardial infarct	P.V.T. (RBBB), P waves not discerned	170	160 152 145 138, Converts to S.R., 100	1,700	

*(RBBB) changed to (LBBB)

P.A.T.: Paroxysmal auricular tachycardia
P.V.T.: Paroxysmal ventricular tachycardia
N.T.: Nodal tachycardia
S.R.: Sinus rhythm

(RBBB): Right bundle branch block pattern
(LBBB): Left bundle branch block pattern
RBBB: Right bundle branch block
LBBB: Left bundle branch block

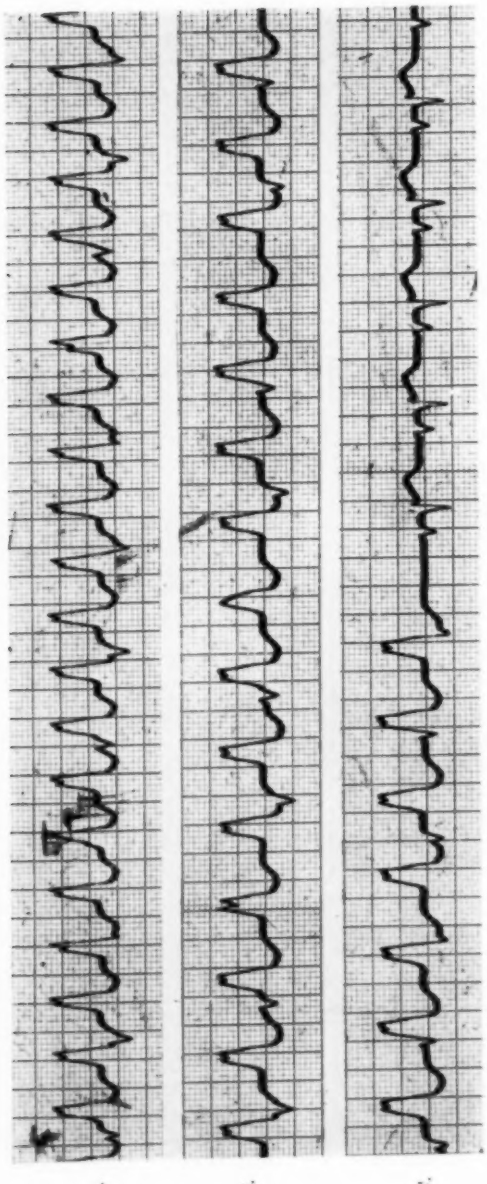

Fig. 3.—Case I$_2$. Lead V$_1$. *A*, Paroxysmal ventricular tachycardia before treatment, rate 155. *B*, After 800 mg. of procaine amide the ventricular tachycardia has slowed to 115. *C*, After 900 mg. of procaine amide the ventricular tachycardia is terminated and sinus mechanism restored.

to cardiac decompensation or sudden death in patients with poor cardiac reserve. Because the tachycardia itself causes these effects, good cardiac reserve cannot be demonstrated until after cessation of the tachycardia. Therefore, all such patients must be treated as if poor cardiac reserve were present.

Intravenous administration of procaine amide has been a quick and relatively safe means of terminating paroxysmal tachycardia. The rapid response of the heart to this agent affords an opportunity to observe closely changes on the direct-writing electrocardiograph. These changes during therapy may clarify the diagnosis of a tachycardic patient whose origin was previously hidden.

The effectiveness of procaine amide varies in different types of paroxysmal tachycardias. The reported experiences with this agent administered intravenously have been summarized with our results in Table IV. Our results are similar to those previously reported except for our greater success in suppressing ventricular tachycardia. Our correction of 100 per cent of the episodes of ventricular tachycardia can be explained by the use of higher doses of procaine amide when necessary than has generally been employed.

TABLE IV. TACHYCARDIAS TREATED WITH PROCAINE AMIDE INTRAVENOUSLY

	REFERENCES	NUMBER OF EPISODES	NUMBER OF PATIENTS	NUMBER OF SUCCESSES	NUMBER OF FAILURES	DOSE OF PROCAINE AMIDE INTRAVENOUSLY (MG.)
Supraventricular tachycardia	1-9	50	41	32	18	160–2000
	This report	13	12	10	3	100–2900
	Total	63	53	42	21	
Auricular flutter	1, 2, 3, 5, 6, 7, 8, 10	34	29	2	32	100–1500
	This report	8	8	0	8	700–3000
	Total	42	37	2	40	
Ventricular tachycardia	1-9, 11-18	86	65	70	16	60–2250
	This report	20	14	20	0	200–2500
	Total	106	79	90	16	

Supraventricular Tachycardias.—Procaine amide was effective in ten of thirteen episodes (77 per cent) of supraventricular (auricular or nodal) tachycardias. Seven of these ten were converted with 500 mg. or less, the other three requiring doses of 800, 1,000, and 1,400 mg. Only one of these patients (Case 10) developed hypotension at 800 mg. which was corrected by administration of *l*-norepinephrine. The three patients who failed to convert were administered higher doses (1,600, 1,700, and 2,900 mg.) and failure was because of hypotension. It appears that hypotension occurs only at higher doses. If procaine amide is the first agent used in treatment, the occurrence of hypotension is reason enough to interrupt its administration and substitute another of the medications known to be effective in supraventricular tachycardia. However, if the tachycardia has

previously failed to convert to sinus rhythm on other medications, and procaine amide is then used,then the hypotension should be corrected by *l*-norepinephrine before continuation of treatment. Of the patients with supraventricular tachycardia, death subsequently occurred in two patients with severe arteriosclerotic heart disease, and in one patient with cirrhosis and cholemia.

Auricular Flutter.—In all patients, procaine amide in doses ranging from 700 to 3,000 mg. was ineffective in terminating this arrhythmia. The dose of procaine amide administered was limited by the occurrence of hypotension in all cases except one in which convulsions occurred (see case report in Appendix). The auricular rate was consistently slowed by treatment. That the auricular rate may be markedly slowed without conversion is demonstrated in Case 18 in which administration of 3,000 mg. of procaine amide slowed the auricular flutter rate from 270 to 115.

A danger in treatment of auricular flutter is illustrated in Case 16 in which there occurred a sudden increase in ventricular rate from 115 to 205 with the slowing of the auricular rate. This abrupt change from a 2:1 to 1:1 A-V conduction resulted from the greater nodal recovery time between auricular impulses. This serious increase in ventricular rate may cause vascular collapse.

In view of the failure to convert the auricular flutter, and the danger of sudden deleterious increases of ventricular rate, intravenously administered procaine amide has no place in the treatment of this arrhythmia. The value of procaine amide as a diagnostic aid between paroxysmal ventricular tachycardia and auricular flutter with bundle branch block has been discussed.[21]

Ventricular Tachycardia.—The episodes of intermittent paroxysmal ventricular tachycardia in three patients were suppressed by 400 mg. or less of procaine amide. All seventeen episodes of persistent paroxysmal ventricular tachycardia in thirteen patients were terminated on doses ranging from 300 to 2,500 mg. Seven of these required more than 1,000 mg., the usually recommended dose.

Ventricular tachycardia in this series was associated with organic heart disease in all but one instance. In nine of the sixteen patients with organic heart disease, an acute myocardial infarction was demonstrated by serial postconversion electrocardiograms.

Seven of the sixteen patients with ventricular tachycardia died 2 to 10 days after treatment with procaine amide without known recurrence of this arrhythmia. In these cases, in spite of temporary improvement resulting from the correction of the rapid heart action, death presumably resulted from the underlying heart disease. It must be emphasized that most of these patients were very ill when first seen, and that this high mortality rate occurred in spite of termination of the tachycardia. Certainly then, in such cases, the additional hazard of rapid heart action must be terminated if survival of the patient is to be hoped for. Procaine amide has terminated all ventricular tachycardias in our experience. In the majority of instances this is accomplished without significant hypotensive changes. Should hypotension develop during the intravenous administration of procaine amide the use of *l*-norepinephrine in quantities empirically found necessary to correct the hypotension will allow the administration of enough procaine amide to terminate the ventricular tachycardia

(Cases 24_3, 25, 32). Should the patient initially be in a state of shock, *l*-norepinephrine can be started before and continued during procaine amide therapy (Case 29).

Thus, it is believed that procaine amide is an excellent agent for the treatment of paroxysmal ventricular tachycardia. It must be emphasized that much larger doses than the usually recommended 1,000 mg. may be necessary to terminate the tachycardia, and that this may be accomplished by the use of *l*-norepinephrine to correct hypotension as it occurs.

TOXICITY

In this series, the toxicity of intravenously administered procaine amide included hypotension, convulsions, and widening of the QRS complexes.

Hypotension when it occurs is not precipitous in onset and is related to the rate of administration and total dose. If the administration is interrupted, the blood pressure tends to return to its previous level, less so at higher than at lower total doses. This hypotension can be controlled by the constant infusion of *l*-norepinephrine, judging the rate of infusion by the blood pressure response.

Convulsions occurred in one patient, as has been reported elsewhere, followed by death 6 hours later. The procaine amide therapy may have been contributory to the death of this patient (see case report, Appendix). After this episode, all patients treated with procaine amide were first given 100 mg. of sodium phenobarbital, intramuscularly.

Gradual widening of the QRS complexes regularly occurred simultaneously with slowing of ventricular response in both supraventricular and ventricular tachycardias. It is believed that this is evidence of the general depressing effect of procaine amide and should not be considered as a contraindication to continuing therapy per se. On the other hand, alteration of the normal QRS to a bundle branch block type of QRS is considered by us to be more significant.

SUMMARY

1. Thirty-three patients with forty episodes of paroxysmal tachycardia were treated with procaine amide administered intravenously.

2. Ten of thirteen episodes of supraventricular tachycardia were converted to sinus rhythm. None of eight episodes of auricular flutter treated were converted. The ectopic focus was suppressed in all of twenty episodes of ventricular tachycardia treated.

3. Hypotension and widening of the QRS complexes were noted. Hypotension was controlled by infusions of *l*-norepinephrine. Convulsions and death in one instance followed procaine amide therapy.

APPENDIX

Case Report.—A 58-year-old male (a chronic alcoholic) was admitted to the hospital because of palpitation and slight dyspnea. There was no history of heart disease. Examination revealed a regular apical rate of 150; blood pressure, 95/80 mm. Hg. There was slight scleral icterus; the liver was palpable 3 cm. below the costal margin. An electrocardiogram revealed an auricular flutter, auricular rate 300 with 2:1 atrioventricular conduction. Intravenous Pronestyl was administered at a rate of 100 mg. per minute. After 400 mg., the auricular rate had decreased to 260, the ventricular rate to 140. After 800 mg. the ventricular rate increased to 160 with frequent aberrant ventricular conduction. After 1,000 mg., the ventricular rate was 180 with all QRS complexes aberrant. The aberrant conduction was associated with the increased rate

of ventricular response. The blood pressure had fallen to 80/60 mm. Hg. Administration of an additional 600 mg. in a ten minute period slowed the ventricular rate to 120, and now the ventricular pattern was of both normal and aberrant conduction. Suddenly the patient became dyspneic and apprehensive. Treatment was stopped. There was no significant change in the electrocardiogram. Three minutes later, the patient had a generalized clonic convulsion lasting about 10 seconds, which was followed two minutes later by a second one. Before each convulsion, a strong pulse was palpable, but neither palpation of the pulse nor registration of complexes electrocardiographically could be obtained during the convulsions. Hence the cardiac mechanism during the convulsions is not known. Following the convulsions the patient was alert and comfortable. As the auricular rate increased after cessation of Pronestyl therapy, the ventricular rate increased to 170 with aberrant intraventricular conduction. This was accompanied by a crushing left chest pain lasting about two minutes. Further increase of auricular rate decreased the atrioventricular conduction ratio, the ventricular rate to 150, and intraventricular conduction became normal. The patient was watched continuously for two hours during which time he was perfectly comfortable. The auricular flutter rate remained at 300 with 2:1 atrioventricular conduction. Six hours later, the patient walked to the washroom, fell to the floor, had a generalized convulsion, and expired. A post-mortem examination was not permitted.

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TREATMENT OF HYPERTENSIVE EMERGENCIES: USE OF VERILOID-IN-OIL* INTRAMUSCULARLY

RALPH V. FORD, M.D., W. R. LIVESAY, M.D., CHARLES SPURR, M.D., AND JOHN H. MOYER, M.D.

HOUSTON, TEX.

ACUTE hypertensive emergencies may be treated by several drugs which are now available, but Veratrum alkaloids remain superior in certain respects. They are just as effective in the supine position as in the upright position, a characteristic which makes them more suitable for the unconscious or bedfast patient. It is always possible to reduce a markedly elevated blood pressure within ten to twenty minutes, using an intravenous infusion of Alkavervir (Veriloid), but constant supervision of the rate of the infusion is required. The inconvenience of this route of drug administration led to an evaluation of the use of repeated injections intramuscularly of an aqueous solution of Veriloid.[1] It was observed that, following a careful titration procedure, the optimal dose could be ascertained which was reproducible on repeated administration at the same dosage level. The duration of significant blood pressure reduction following intramuscular aqueous Veriloid was relatively short, averaging 3 1/4 hours. In an attempt to reduce the frequency of intramuscular administration, the response to Veriloid in a corn-oil depot preparation has been studied in patients with severe hypertension. If such a preparation were found to be clinically effective, the management of hypertensive emergencies would be simplified.

MATERIALS AND METHODS

Intramuscular Veriloid-in-Oil was administered to twenty-four patients with severe hypertension. Eleven of these presented evidence of malignant hypertension (retinal hemorrhages, papilledema, etc.). The pertinent vital statistics of these patients are summarized in Table I. The fundi were graded according to the Keith-Wagener classification. Renal disease was graded 0 to 4+ on the basis of clinical renal function studies which included routine urinalysis, urine concentration test, blood urea nitrogen values, the excretion of phenolsulfonphthalein, and other available clinical information. Those patients with frank uremia were graded 4 and those with minimal renal disease were graded 1. The drug, Veriloid-in-Oil, was given in an incremental dosage fashion to ascertain the optimal dose for the individual patient. The initial dose was arbitrarily selected

From the Cardiac Clinic of the Jefferson Davis Hospital, the Veterans Administration Hospital, and the Departments of Medicine and Pharmacology of Baylor University College of Medicine, Houston, Tex.

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TABLE I. BLOOD PRESSURE AND CLINICAL RESPONSE TO INTRAMUSCULAR VERILOID-IN-OIL

PATIENT	CONTROL B. P.		B. P. MAXIMUM RESPONSE		B. P. REDUCTION		I. M. DOSE (MG.)	SIDE EFFECTS	DIAGNOSIS	FUNDI	RENAL DISEASE	AGE	SYMPTOMS* IMPROVED
	S	D	S	D	ONSET (HR.)	DURATION (HR.)							
S. G.	190	130	120	88	2.25	5+	4	dizzy	HCVD	3	1+	40	Yes
W. B.	170	100	140	80	3	4	2	0	HVD	3	1+	40	Yes
B. M.	200	100	160	98	3	3	3	0	HCVD, HF	2	1+	58	Yes
E. J.	170	110	140	90	3	4	1.5	0	HVD	1	1+	50	No
J. M.	170	110	122	82	4	1	4	N&V	HVD	2	1+	40	Yes
G. S.	170	100	130	80	3	3	3	N&V	HVD	2		40	No
R. L.	230	130	130	88	3.25	9+	6	N&V	MHVD	4	3+	38	Yes
A. V.	230	120	120	70	2	5	3	0	MHVD	4	4+	38	Yes
J. C.	210	118	120	80	1	5+	5	0	HCVD	4	3+	38	No
T. M.	280	160	110	70	1	6	3	0	HCVD	2	0	37	No
A. A.	280	180	130	100	1	8+	7	0	HCVD, HF	3	1+	50	No
V. P.	240	150	150	100	1	7	5	N&V	MHCVD	4	4+	37	Yes
M. C.	180	120	156	94	3.25	9+	3	N&V	MHVD	4	3+	52	Yes
C. B.	220	130	110	60	1	7	4	N&V	MHVD	4	3+	49	Yes
L. F.	220	130	132	72	1	4+	5	0	HCVD	2	0	48	No
J. P.	180	110	120	80	2	6	4	0	HCVD	2	1+	38	No
C. P.	194	116	80	40	1.50	12	2	N&V	HCVD	3	0	34	No
W. G.	250	150	140	80	1	6	2	N&V	MHCVD	4	4	49	No
E. B.	180	110	150	90	2	4+	3	0	HCVD	3	2+	35	Yes
I. P.	240	130	150	100	1	8	2.5	0	MHVD	4	3+	42	Yes
V. J.	220	130	140	90	3	6+	3.5	0	HCVD	3	0	46	No
U. L.	250	150	110	60	0.5	12	2	N&V	MHCVD	4	3+	43	Yes
D. D.	200	120	180	130	1	5+	3.5	0	MHVD	4	2+	43	No
B. C.	220	140	150	90	.5	8	2.0	0	MHCVD	4	3+	41	Yes
Average	212	127	133	84	1.9	6.1	3.5						
Av. Resp. to‡ Aq. Ver. I. M.	214	135	151	90	0.25	3.25	1.5						

S = systolic, D = diastolic } in millimeters of mercury

O = no side effects
N&V = nausea and vomiting
HVD = hypertensive vascular disease
HCVD = hypertensive cardiovascular disease
MHCVD = malignant hypertensive cardiovascular disease
HF = congestive heart failure
Fundi = 0–4+, Keith-Wagener classification
*Symptoms resulting from hypertensive disease
‡Average response to an aqueous preparation of Veriloid administered intramuscularly.[1]

as 2 mg. in most cases and the subsequent doses were adjusted upward in 2 mg. increments until a blood pressure response was observed. Then 0.5 mg. increment was employed until an optimal blood pressure response was obtained. In one instance the 2 mg. dose proved to be excessive and it was necessary to reduce the next dose to 1.5 mg., which was optimal for this patient. The initial doses were usually administered at 24-hour intervals. One patient was given repeated doses within a 24-hour period in an attempt to control the encephalopathic manifestations of terminal hypertensive disease. It was necessary to use atropine in a few instances to combat excessive bradycardia, and in several instances Neo-synephrine or norepinephrine were used because of excessive reduction in blood pressure.

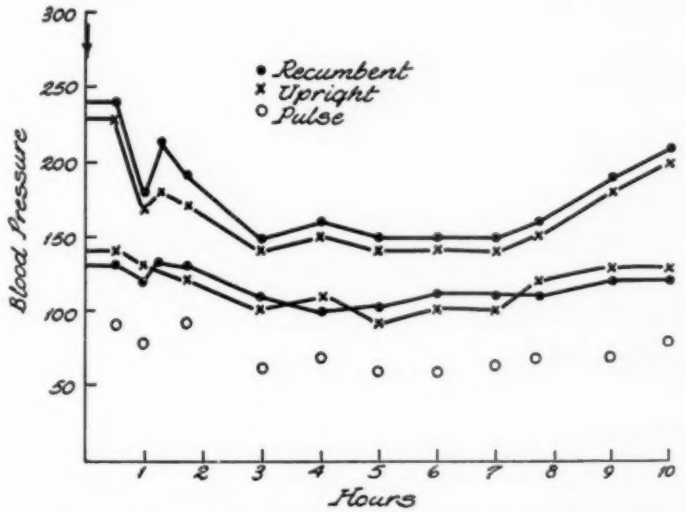

Fig. 1.—Severe uremic hypertensive patient. The typical response to an optimal dose of intramuscular Veriloid-in-Oil. Blood pressure is graphed as systolic and diastolic levels.

RESULTS AND DISCUSSION

A satisfactory hypotensive response was nearly always obtained in patients who received an optimal dose of Veriloid-in-Oil administered intramuscularly. In Table I, patient D.D. received a suboptimal dose and expired prior to the use of a clinically effective dose. A satisfactory hypotensive response at an optimal dose was considered a reduction of the recumbent blood pressure to 150 mm. Hg systolic and 100 diastolic without prohibitive side reactions. There was no evidence of insufficiency in the cerebral or coronary circulation associated with the reduction of the blood pressure. Two patients with uremia showed progression of the renal insufficiency as the blood pressure was reduced and one of them died.

The response in blood pressure and in clinical signs and symptoms is presented in Table I. The average control blood pressure of 212/127 mm. Hg was reduced to 133/84 when an optimal dose of Veriloid-in-Oil was administered. The duration of the hypotensive response varied from one to twelve hours (average, 6.1 hours) and the onset of action occurred between 30 and 240 minutes

(average, 114 minutes or 1.9 hours). The optimal dose varied from 1.5 mg. to 7.0 mg. (average, 3.4 mg.). Symptoms of hypertensive crisis were improved in thirteen of the twenty-four patients, and symptoms were unchanged in the remainder of the patients. At the optimal dose, nine of the twenty-four experienced distressing nausea or vomiting or both, but this was not prohibitive and was usually seen only during the acute phase (10 to 30 minutes) of a marked reduction in blood pressure. Thus, a typical response to an optimal dose of intramuscular Veriloid-in-Oil is illustrated in Fig. 1. The reduction in blood pressure began about one hour after the drug was administered and reached a maximum hypotensive response at three hours. The drug effect decreased and the blood pressure began to rise at eight hours and approached the control level at 10 to 12 hours. No nausea or vomiting was experienced in this particular case.

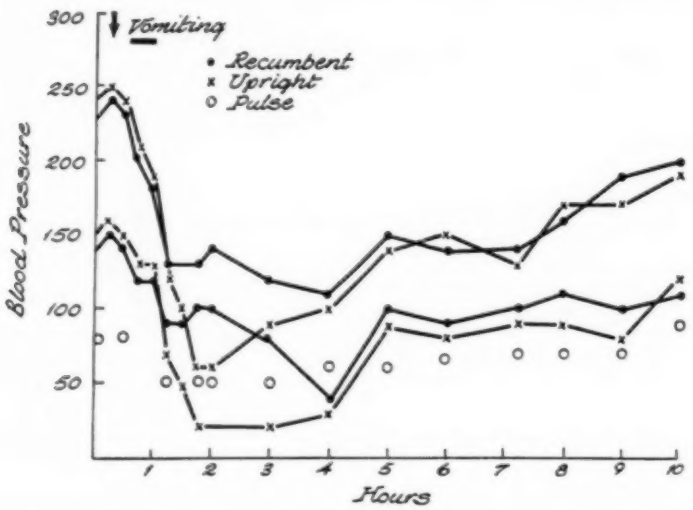

Fig. 2.—Labile hypertensive patient. The typical response to a greater-than-optimal dose of intramuscular Veriloid-in-Oil. There is an additional orthostatic hypotensive effect not seen with the optimal dose. Vomiting is noted during the 30-minute period of precipitous decline in blood pressure (systolic and diastolic levels are graphed).

A typical response to a greater than optimal dose of intramuscular Veriloid-in-Oil is illustrated in Fig. 2. The reduction in blood pressure began 30 minutes after the dose was administered and reached a maximum response in two hours during which time severe nausea and vomiting were experienced. Also, with this dose, there was an additional decline in blood pressure in the upright position over the recumbent position (orthostatic response). This effect is not seen with an optimal dose. The total duration of action was somewhat greater than with an optimal dose.

The response to increasing doses of intramuscular Veriloid-in-Oil and the reproducibility of optimal doses on successive days are presented in Table II. Reproducibility seemed adequate, but, as with aqueous intramuscular Veriloid, it is quite obvious that in the responsive range the dose is quite critical. This emphasized the necessity for carefully measuring the dose of the drug since

TABLE II. RESPONSE TO VERILOID-IN-OIL INTRAMUSCULARLY. A COMPARISON OF RESPONSIVENESS TO INCREASING DOSES AND REPEATING THE SAME DOSE ON DIFFERENT DAYS

PATIENT	CONTROL B. P.		B. P. MAXIMUM RESPONSE		B. P. REDUCTION		I. M. DOSE (MG.)	SIDE EFFECTS
	S	D	S	D	ONSET (HR.)	DURATION (HR.)		
B. M.	200	100	160	98	3	3	3.0	0
	210	110	180	100	3	1	4.0	0
	228	116	160	100	3	4	5.0	0
	230	120	110	70	3	6	6.0	N&V
A. A.	300	210	160	100	3	2	4.0	0
	284	190	148	98	2	8	6.0	0
	280	180	130	100	1	8+	7.0	0
L. F.	240	150	240	150	—	—	2.0	0
	220	130	160	120	3	1	4.0	0
	220	130	110	60	1	6	5.0	N&V
	220	130	132	72	1	4+	5.0	0
E. B.	180	110	150	90	2	4+	3.0	0
	180	100	180	100	—	—	3.5	0
	200	120	150	100	2	8	4.0	N&V
	190	118	148	98	2	9	4.0	0
A. V.	230	120	120	70	2	5	3.0	0
	220	110	90	60	2	5	3.0	0
	280	160	110	70	1	6	3.0	0
	260	148	118	80	2	7	3.0	0
J. P.	210	120	210	120	—	—	3.5	0
	210	120	150	110	1	7	4.0	N&V
	180	110	120	80	2	6	4.0	0
	200	118	130	88	2	8	4.0	0

S = systolic, D = diastolic } in millimeters of mercury

0 = no side effects
N&V = nausea and vomiting

amounts only slightly in excess of the optimal dose produce an excessive blood pressure reduction with prohibitive side reactions. In one patient, illustrated in Fig. 3, consistent hypotensive responses were elicited by identical doses administered every eight hours, but vomiting was quite prominent. The dose was decreased by 0.5 mg. and administered every six hours, but the period of rapid decline in blood pressure continued to be associated with vomiting. After a 24-hour interval, in which the patient did not receive any form of medication, hexamethonium was injected subcutaneously every four to six hours at a dose of 12.5 mg. to 25 mg. The reduction in blood pressure was smoother and vomiting was not experienced, but there was a rapid appearance of oliguria associated with progression of the uremia and the patient expired. This case emphasizes the disadvantage of decreasing the blood pressure in the presence of marked renal impairment because of the frequent occurrence of exceeding the critical (minimal) level of blood pressure required for filtration at the glomerulus, a situation more frequently encountered with adrenergic and ganglionic blocking agents than with drugs (Veriloid) which act within the cephalic region.

Thus, the results with intramuscular Veriloid-in-Oil are quite similar to the results with intramuscular aqueous Veriloid except that the duration of action was longer with the depot preparation, thus requiring fewer injections. However, as with intramuscular aqueous Veriloid, intramuscular Veriloid-in-Oil produces a less consistent blood pressure regulation than intravenous Veriloid, probably a result of the narrow therapeutic index of Veratrum and a more variable blood level following the intramuscular route of administration by comparison to the intravenous route. Individual patients require a critical adjustment of dose. Once that optimal dose has been established it is necessary

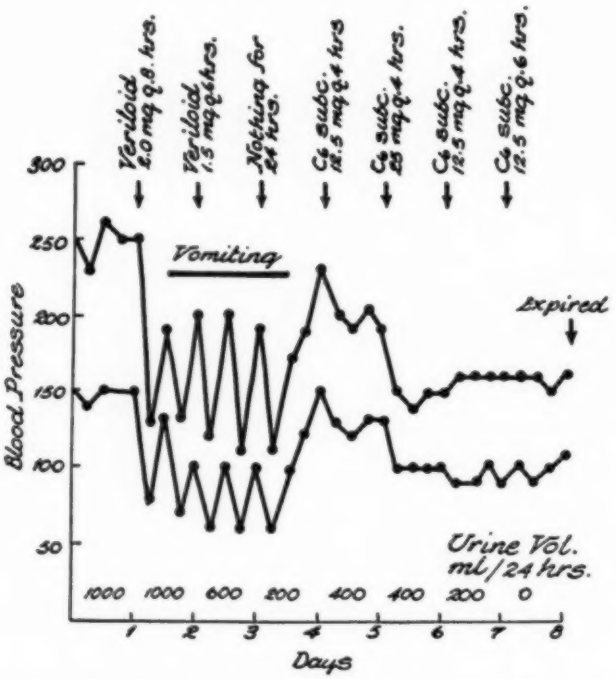

Fig. 3.—Malignant nephrosclerosis. Comparison of blood pressure (systolic and diastolic levels) response to Veriloid-in-Oil intramuscularly for three days followed by the response to hexamethonium subcutaneously after an interval of 24 hours.

also to vary the period between drug administration so that excessive reduction in blood pressure does not occur because of overlapping blood levels from previous drug administration. The use of the antiemetic agent, Chlorpromazine, may be of value when used concurrently with Veratrum preparations. When used prior to Veratrum, the incidence and severity of Veratrum-induced vomiting were reduced in half, in both animals[2] and human patients.[3]

SUMMARY AND CONCLUSIONS

Intramuscular Veriloid-in-Oil is consistently effective in reducing the blood pressure in patients with hypertensive emergencies. This depot-type preparation allows for less frequent administration of doses than does the aqueous intramuscu-

lar preparation of Veriloid. Since nausea and vomiting are the most frequent distressing side reactions to Veriloid in any form and, since these occur predominantly during the acute phase of blood pressure reduction immediately after the drug administration, it is only reasonable that a slower and longer acting form of Veriloid would be associated with less nausea and vomiting. However, both aqueous and depot Veriloid suffer the disadvantage of a less consistent and reproducible effect than does intravenous Veriloid. The latter, however, presents the distinct disadvantage of requiring constant supervision of the rate of infusion. Each patient requires individual adjustment of dose and time intervals between doses. The average optimal dose of Veriloid-in-Oil in this study was 3.5 mg.. the average onset of action was 114 minutes (1.9 hours), and the average duration of action was 366 minutes (6.1 hours). In a previous study, the average optimal dose of aqueous intramuscular Veriloid was 1.5 mg., the average onset of action was 16 minutes (¼ hour), and the average duration of action was 196 minutes (3¼ hours).

It is therefore recommended that the patient with a hypertensive crisis, in the absence of constant supervision, receive injections of intramuscular Veriloid-in-Oil at 12-hour intervals, beginning with 2 mg. and adjusting the dose upward or downward at 0.5 mg. increments until an optimal dose has been established, i.e., one which produces a satisfactory reduction in blood pressure without prohibitive side reactions. Once this dose has been established, the time interval may be adjusted to give maximum hypotensive coverage, remembering the latent period between administration and onset of effect.

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PERFORATION OF THE INTERVENTRICULAR SEPTUM

Report of Three Cases With Ante-Mortem Diagnoses

A. A. Goetz, M.D., and A. N. Gropper, M.D.

San Francisco, Calif.

RUPTURED interventricular septum may be due to infectious or traumatic causes but is most often a complication of myocardial infarction. Review of the literature reveals seventy-five cases of ruptured interventricular septum following infarction, in only thirty of which the diagnosis was made before death. This pathologic entity has been recognized for over 100 years.[1]

In the following three cases (admitted to Mount Zion Hospital in the last 7 years) the diagnosis was made before death in all.

CASE REPORTS

Case 1.—E.L., a 56-year-old white man, was admitted Oct. 4, 1944, complaining of increasing substernal pressure, radiating to the throat, of one-week duration, associated with weakness, dyspnea, and headache. Past history was not remarkable, and no previous cardiac disease was disclosed.

Physical examination revealed a pallid, listless man with blood pressure of 150/100 mm. Hg, pulse 88, temperature 37.4°C. Heart sounds were distant, and a gallop rhythm was heard. The lungs were clear.

The white blood cell count was 8,900 per cu. mm. with 92 per cent polys; the erythrocyte sedimentation rate (Wintrobe) 25 mm. per hour. Urinalysis disclosed a 1-plus test for albumin and a specific gravity of 1.017.

On the following day, increasing listlessness, and a blood pressure of 100/75 mm. Hg; irregular pulse 56 to 60 per minute was noted as was the appearance of a loud systolic murmur over the precordium, maximal at the tricuspid area. A few basilar pulmonary râles were also audible. The diagnosis of ruptured interventricular septum was made. Electrocardiogram (Fig. 1) that day showed posterior myocardial infarction with deep Q_2, Q_3 waves, inverted T_2 and T_3, elevated $S\text{-}T_2$ and $S\text{-}T_3$, and complete auriculoventricular block.

On Oct. 6, the electrocardiographic complexes were unchanged, but a Wenckebach type block was now present. X-ray of the chest disclosed the heart to be enlarged and a small amount of fluid at the lung bases. On Oct. 7, a short diastolic murmur was audible along the left sternal border, which aroused suspicion that a ventricular aneurysm might be present. On Oct. 12, sinus rhythm was seen in the electrocardiogram; there was first-degree block with a P-R interval of 0.26 sec., the QRS complexes were lower in voltage and the S-T segments approached the isoelectric line. Two days later the white blood cell count rose to 19,000 per cu. mm. On Oct. 17, the rhythm was auricular fibrillation. The patient became anuric, developed increasing pulmonary edema with superimposed pneumonia and fever varying from 38 to 40°C. He expired Oct. 24.

From the Department of Medicine, Mount Zion Hospital, San Francisco, Calif.
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Necropsy showed the heart to weigh 340 grams. The septum and the posterior walls of the left and right ventricles were soft. The entire posterior wall of the left ventricle was pouched backward to form a sac 6.5 cm. in greatest diameter, which extended upward to the base of the aortic valve, and downward to within 1 cm. of the apex; this sac also extended to the lateral margin of the heart, and in the other direction to the interventricular septum. The entire septum was involved with the exception of the anterior portion 2 cm. wide. At the posterior margin of the septum, midway between the base and apex of the heart, a rounded defect was found, 1 cm. in diameter, communicating with the cavity of the right ventricle. The valves were normal. The coronary ostia were patent but small. The right circumflex artery was occluded by a fresh clot 1 cm. from its origin. The left anterior descending artery was occluded 1.5 cm. from its origin by a dense fibrous material. The left circumflex artery was small.

The anatomic diagnoses were coronary arteriosclerosis, old occlusion of the left anterior descending artery, recent occlusion of the right coronary artery, hypoplasia of the left circumflex artery, recent massive myocardial infarction with rupture of the interventricular septum, chronic passive congestion of all organs, right hydrothorax, and bilateral broncho-pneumonia.

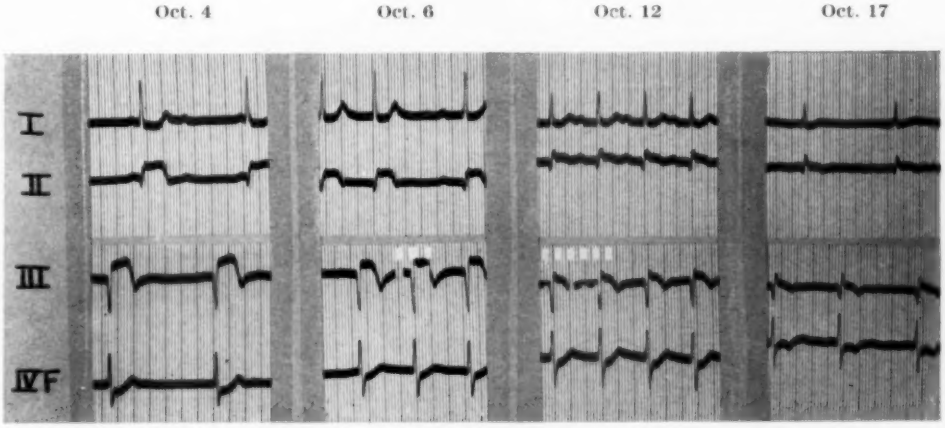

Fig. 1.—Case 1. Serial electrocardiograms demonstrating the Q_3T_3 pattern of posterior myocardial infarction and the variation of heart block from complete to first degree, and finally auricular fibrillation.

CASE 2.—P.C., a 58-year-old white woman, was admitted Feb. 11, 1947, complaining of severe precordial pressure and pain, radiating from the left scapula to the left precordium of several hours' duration, somewhat relieved by an injection of morphine sulphate. The pain persisted in milder form until admission (about 1 day) and was slightly increased with respiration. She had suffered two attacks of emesis and persistent nausea. Her past history and system review were negative, except that her blood pressure was recorded the night before admission as 200/90 mm. Hg.

Physical examination showed an ashen-colored small woman in some pain. The blood pressure was 150/70 mm. Hg, pulse 110, and temperature 37.4°C. The heart was slightly enlarged with the point of maximal impulse in the fifth intercostal space 8 cm. to the left of the sternum. The rhythm was regular, and a harsh high-pitched systolic murmur was heard at the left central precordium with no associated thrill. The aortic second sound was absent. Râles were audible at both bases and the liver was palpable 5 cm. below the right costal margin. There was no peripheral edema. Diagnoses of arteriosclerotic heart disease, coronary arteriosclerosis, and acute myocardial infarction were made. The possibility that a perforation of the interventricular septum had occurred was also suggested.

The white blood count was 8,500 per cu. mm. with 78 per cent polys; the erythrocyte sedimentation rate was 16 mm. per hour (Wintrobe). The urine showed a 2-plus test for albumin and occasional hyaline casts.

Electrocardiogram, Feb. 11, (Fig. 2) showed sinus rhythm, rate 95 per minute; P-R interval of 0.14 sec., flattened T_I, markedly elevated S-T_{CF4}, and splintered Q-S_{CF4}. This was interpreted as suggesting acute anterior myocardial infarction. An electrocardiogram on the following day was unchanged in the same leads. Additional unipolar precordial leads, however, confirmed the presence of an acute anteroseptal myocardial infarction. Chest x-ray was reported as showing

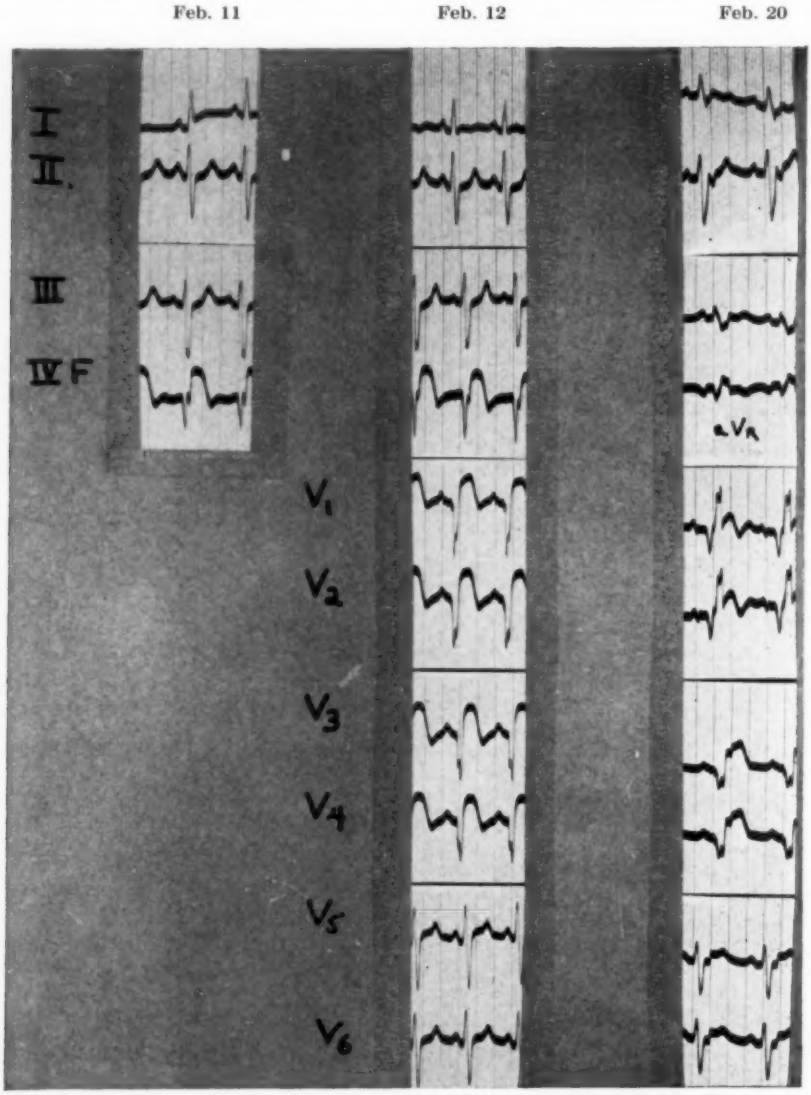

Fig. 2.—Case 2. Electrocardiogram showing marked S-T elevations and absence of R waves in precordial Leads V_1 to V_4 indicative of anteroseptal infarction. Marked change of pattern on Feb. 20 to that of right bundle branch block (see text).

the heart enlarged. A gradually increasing oliguria developed, and the patient became more lethargic. An electrocardiogram Feb. 20, revealed the QRS complexes broadened to 0.20 sec. and right bundle branch block. That night there were signs of increased venous pressure and the patient expired.

At necropsy, the heart weighed 360 grams, and an area 4 x 5 cm. over the apex was soft. The interventricular septum presented a funnel-shaped thinned area, at the bottom of which a

perforation extended into the right ventricle (Fig. 3). The coronary vessels were sclerotic and the left anterior descending artery was occluded in the vicinity of its origin by fresh clot. The valves were intact.

The anatomic diagnoses were: coronary arteriosclerosis, severe, with acute occlusion of the left anterior descending coronary artery and acute myocardial infarction; rupture of the interventricular septum; congestive failure with congestion of the lungs, liver, spleen and other viscera.

CASE 3.—R.S., a 76-year-old white woman, entered the hospital Feb. 13, 1951, complaining of severe substernal aching pain with radiation to the left arm, present for 24 hours, and increasing in intensity just prior to admission. There were no cardiovascular symptoms in her past history and her blood pressure had once been recorded at 120/90 mm. Hg.

Fig. 3.—Case 2. Probe extends from the left into the right ventricle through the septal rupture.

Physical examination revealed an obese white female appearing fairly comfortable. Blood pressure was 140/82 mm. Hg, pulse 72, temperature 37.4°C.

The point of maximal cardiac impulse was in the fifth intercostal space at the mid-clavicular line. The second aortic sound was louder than the second pulmonic sound; heart tones were muffled. No murmurs or thrills were heard. The liver was not palpable nor were peripheral edema or cyanosis seen. Diagnosis of arteriosclerotic disease with acute myocardial infarction was made.

The leukocyte count was 7,700 per cu. mm. with 72 per cent polys; the erythrocyte sedimentation rate was 33 mm. (Wintrobe). On the following day an electrocardiogram (Fig. 4) disclosed flattening of T waves in II, V_5 and V_6, and T inversion in III; S-T segment was elevated in III, aV_F and aV_R and depressed in I and aV_L. The tracing was interpreted as suggestive of posterior myocardial infarction.

At first she responded to bed rest and routine therapy. She was asymptomatic until Feb. 18, at which time the severe precordial pain recurred accompanied by nausea and retching. The blood pressure was 125/80 mm. Hg, but shortly dropped to 80/0, when signs of shock became evident. Stimulants and narcotics restored her blood pressure to 125/90 mm. Hg, and her condition temporarily improved, although the chest pain continued. A loud, rough systolic murmur and thrill were now heard. The murmur was present throughout the precordium, but maximal in the fourth intercostal space at the left sternal border. Pulmonary basilar râles were now present. Diagnosis of rupture of the interventricular septum subsequent to posterior myocardial infarction was made.

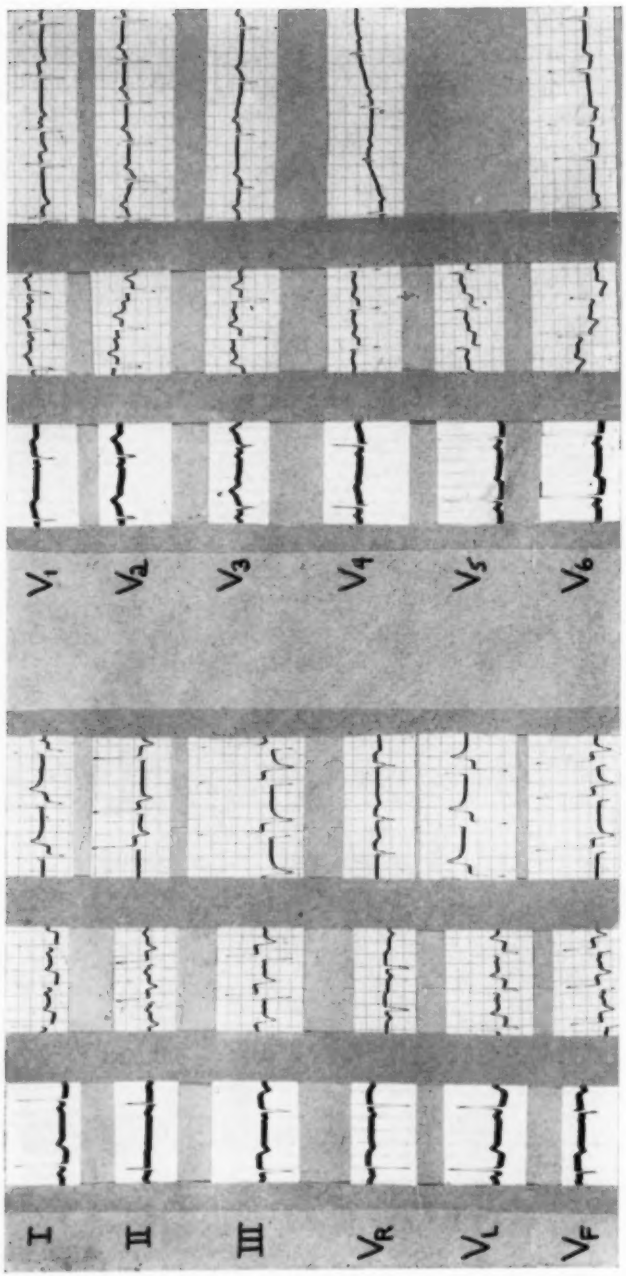

Fig. 4.—Case 3. Note pattern of posterior infarction on Feb. 14; exaggeration of the ST-T changes on Feb. 18 and distinct beginning change in axis deviation toward the right. Pattern on Feb. 19 reveals fully developed right ventricular strain and nodal rhythm.

An electrocardiogram now showed marked S-T depression in I and V_L; and elevation in II, III, and aV_F with late deeper inversion of the T waves in these leads; depressed S-T segments in V_3, V_4, V_5 and V_6 followed by diphasic T waves. The interpretation was posterior myocardial infarction with possible anterolateral ischemia.

The following day, Feb. 19, an electrocardiogram showed atrioventricular nodal rhythm, rate 72. The most striking changes consisted of a shift of the electrical axis toward the right in the standard leads shown by the appearance of an S in I, and a tall R in III. Deep, wide Q waves were now present in V_1 and V_2, and R waves now followed the Q waves. The intrinsicoid deflection time measured 0.06 sec. in V_1. The T waves, previously inverted, were now deeper. The electrocardiogram was interpreted as consistent with right ventricular strain superimposed on posterior myocardial infarction.

Despite intensive therapeutic measures, nausea and pain continued, and the patient expired on Feb. 20, 1951.

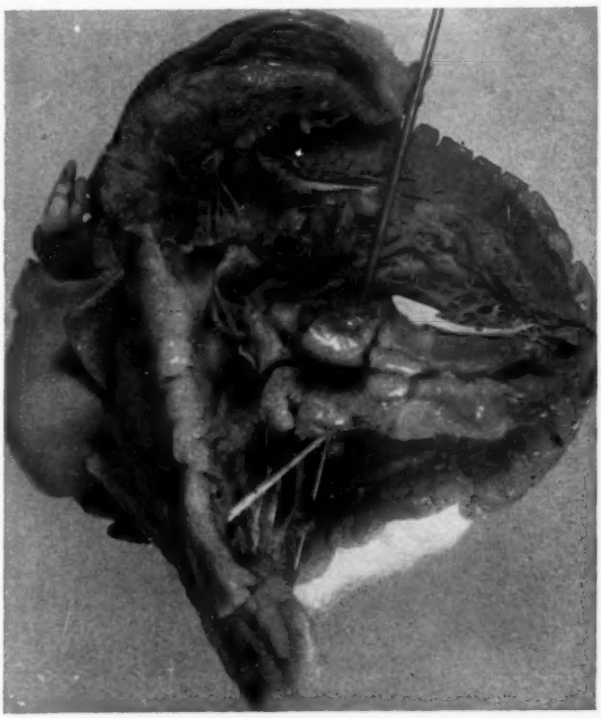

Fig. 5.—Case 3. Probe is placed in a rent 1.5 x 0.5 cm. in the posterior portion of the septum.

At *necropsy* the heart weighed 480 grams. There were softening and ecchymosis over the posterior heart in the area of the interventricular septum that involved both the left and right ventricular myocardium. On section, the infarction spread into the posterior interventricular septum. A thrombus occupied a defect which measured 1.5 x 0.5 cm., in the interventricular septum (Fig. 5).

The valves were not unusual. The coronary vessels showed areas of sclerosis and stenosis the most marked being in the left anterior descending artery, 1 cm. from its origin. There were similar areas in the circumflex and posterior coronary vessels.

The anatomic diagnoses were: generalized arteriosclerosis, coronary atherosclerosis with arteriosclerosis and stenosis of the left anterior descending artery and sclerosis of the circumflex and posterior arteries; recent acute infarction of the posterior right and left ventricular musculature with extension into the posterior interventricular septum; rupture of the interventricular septum at the infarction site; terminal bronchopneumonia.

DISCUSSION

The advent of the rupture of the interventricular septum is heralded clinically by sudden decline of the patient's condition, evidenced by pain, tachycardia, dyspnea, nausea, vomiting, signs of right and/or left-sided heart failure and shock. Therefore, it is not unlike many of the complications which may plague the patient with myocardial infarction; such as, extension of the infarction, pulmonary embolus and arrhythmias. The guide to the diagnosis is the sudden appearance of the harsh systolic murmur described variously as best heard at the fourth left intercostal space, lower sternum, or apex. The murmur is produced equally readily by pinpoint or large septal rents. A diastolic murmur is also occasionally heard. This may arise from the development of a concomitant ventricular aneurysm, such as was present in Case 1, and which Moolton[2] also described in his case report. A systolic thrill is frequently palpated. Elevation or depression of the blood pressure, and the presence or absence of congestive failure apparently have little to do with the intensity of the murmur.

The area of infarction with involvement of the septum may extend from either the anterior or the posterior walls. In twenty-five cases reviewed since 1942, including our patients, the posterior wall was involved alone in eight, the anterior wall in twelve, and both the anterior and the posterior walls in the other five instances. The left anterior descending artery was the artery most frequently occluded, but regardless of the site of occlusion, sclerosis and narrowing of the other vessels were almost invariably present. Blumgart[3] showed that three basic types of coronary artery supply to the septum and heart exist: (1) the balanced coronary flow in 40 per cent, (2) left coronary artery preponderance in 20 per cent, (3) right coronary artery preponderance in 40 per cent. This distribution appeared to favor posterior infarctions; however, Blumgart[3] also stated that "The site of occlusion or occlusions in the coronary arteries bear no necessarily constant or immediately obvious relationship to the location of the infarction in the heart." Especially in the presence of generalized coronary arteriosclerosis, it is not unusual or unexpected that posterior infarction resulted frequently from occlusion of the left coronary artery.

The perforations are single or multiple and are most often located toward the apex and posteriorly, which may account for the relative lack of disturbance in the conduction mechanism.

There were 145 recent myocardial infarctions found in 1,292 consecutive autopsies performed at Mount Zion Hospital during the years 1940 to 1951. Ruptures of the heart occurred in fourteen cases. These involved the left ventricular wall in eleven and the interventricular septum in three, which are reported here. Ruptures represented 9.6 per cent of the cases with recent infarctions which is in close agreement with larger series reported. Edmondson and Hoxie[4] found myocardial rupture in 72 of 865 cases of unhealed infarction. This approximates closely the figure of Friedman and White[5] of 9.5 per cent. The incidence in mental institutions is much higher; one series[6] demonstrated sixteen cases of rupture in twenty-two acute myocardial infarctions, implying that mental patients apparently fail to recognize or report the heart attack and so, with continued activity, the incidence of rupture is much higher. According to

Sager,[7] 3 per cent of nontraumatic ruptures are through the septum, yet Edmondson and Hoxie[4] found thirteen cases in seventy-two ruptures were septal, an incidence of 18 per cent.

The time interval between infarction and rupture has been averaged as 7.4 days with 98 per cent occurring by the sixteenth day.[4] These figures correlate closely with the progression of necrotic and degenerative changes in the infarcted area as described by Mallory and associates.[8]

Differing from ventricular rupture, survival after septal rupture may be prolonged, as in the unique patient of Wood and Livezey[9] who lived four years and ten months after perforation of the septum. However, of the fifty-seven cases which survived less than one month, the average duration of life was 7.6 days. Our cases survived 2, 9, and 19 days, respectively, after rupture.

It has been difficult, so far, to establish an electrocardiographic pattern which would be helpful in substantiating the diagnosis of ruptured interventricular septum. This may be due to the lack of electrocardiographic material published. Roesler and Dressler[10] searched the literature and found the majority of case reports included either no electrocardiograms, or only three standard leads. They found only two in which, in addition to standard leads, Lead IV_F was available. Since then, we have found only nine published electrocardiographic reports which include multiple chest leads showing signs of septal infarction. In three of these[19-21] and our Cases 2 and 3, in serial tracings after the occurrence of perforation, right bundle branch block patterns ensued. This may be interpreted as reflecting sudden development of right ventricular strain.

Electrocardiographic patterns simply indicating anterior or posterior infarctions have been noted. However, several authors[10,11] comment that the pattern of posterior infarction, that is Q_3-T_3 inversions and S-T_3 elevations, combined with diagnostic signs of infarction in the precordial leads point to septal infarction extending from the anterior to the posterior ventricular walls. Axis deviation may be to the left but is more often described as to the right, resulting from the increasing right ventricular strain. Master and Russell[10] reported one case in which the septum was herniated for a distance of 2.5 cm. into the right ventricle, producing a Bernheim syndrome, and was electrocardiographically portrayed by progressive right-axis deviation. In Case 3 above, a similar chain of events probably induced the right bundle branch block pattern seen in the final tracing.

In a series of 164 cases of myocardial infarction reviewed by Myers and associates,[12] a high percentage (63 per cent) showed septal involvement. Tracings showing prolonged QRS complexes with a pattern resembling right bundle branch block and several of left bundle branch blocks were described. A QS type complex and a triphasic QRS were seen in V_1 and V_2. Elevations of the RS-T segments, dependent on the site of infarction, were commented upon by him.

Thirty-five cases of myocardial infarction were autopsied by Osher and Wolff,[22] who found the septum involved in thirty-two cases. They reviewed the electrocardiographic patterns in those in which the septum was infarcted and concluded that the most common feature was a conduction defect. They considered a diagnosis of septal infarction could be made (a) when bundle branch block or high grade auriculoventricular block appeared during the course of acute myo-

cardial infarction; (b) when right bundle branch block was associated with conspicuous Q waves in the right precordial leads; (c) when left bundle branch block was associated with Q waves in the left precordial leads; and (d) when left bundle branch block was associated with low voltage in the limb and left precordial leads. QS deflections with abnormal elevation of the S-T segments in the right precordial leads of the electrocardiograms displaying normal interventricular conduction were deemed fairly reliable evidence of acute septal infarction. Characteristic of septal infarction was an electrocardiographic pattern of simultaneous anterior and posterior myocardial infarction, which, however, occurred relatively infrequently.

Disturbances of rhythm other than ectopic beats are only occasionally noted. Auricular flutter,[11] interference dissociation,[13] complete auriculoventricular block and transient nodal tachycardia[12] have been observed and are more likely to occur in posterior infarctions extending into the base of the septum. This more frequent disturbance of atrioventricular conduction and rhythm in cases of posterior infarctions is best explained by the fact that the blood supply to the atrioventricular node is derived from a branch of the posterior coronary artery.[14] This is in accord with the arrhythmias found in Cases 1 and 3, both of which had posterior infarctions. In the former, complete and variable degrees of auriculoventricular block and finally auricular fibrillation developed, and in the latter a nodal arrhythmia was observed.

The onset of ruptured interventricular septum is to be differentiated from infarction superimposed on congenital intraventricular defect, and from tearing of the chordae tendineae or papillary muscle. In Askey's recent review[15] of thirty-seven cases of ruptured papillary muscle, significant points of differentiation from perforation of the septum were the relative infrequency of the systolic murmur, the somewhat greater incidence of diastolic murmurs, and the total absence of a thrill in the patients with papillary muscle tear. Also, in papillary muscle disease, the abnormal auscultatory signs were more common over the cardiac apex, and the traumatic event lead to sudden development of left-sided heart failure and collapse.

Septal ruptures are relatively infrequent which may be because the septum provides a zone of anastomosis between the right and left coronary arteries.[16] Yet, it is exposed to a great degree of stress in the cardiac cycle, maintaining the pressure differential between the right and left ventricle, shortening and partaking in the systolic contraction. Moolten[2] observes that the septal musculature is composed of three of the six cardiac muscle bundles and feels that injury to any of these has an excellent prospect of being transmitted to the septum; and, also, the transmission may operate in the opposite direction depending on the site of injury. This may lead to incapacity of septal function in injury to the ventricular muscle, or ventricular impairment in damage to the septal musculature. However, perhaps this extended relationship may better be visualized on the basis of the work of Blumgart and associates.[3]

Edmondson and Hoxie[4] introduced figures indicating that unscarred hearts rupture about four times as often as scarred hearts. Correlation with blood pressure was not clear-cut, and their conclusion was that collateral circulation in

the unscarred hearts was not as advanced, thus favoring rupture. This is also borne out by the relatively rare occurrence of rupture of ventricular aneurysm.[17]

In 1931, Sutton and Davis[18] demonstrated that cardiac aneurysms were more likely to develop in animals which were exercised shortly after myocardial infarction was produced. It seems obvious that this also should influence the physician in trying to avoid other complications of myocardial infarction, such as perforation of the intraventricular septum, and, therefore, in spite of the growing recent enthusiasm toward earlier ambulation of the patient with myocardial infarction, it would seem that two to three weeks of bed rest is indicated along with all possible measures to enhance collateral coronary blood flow.

SUMMARY

Three additional cases of perforation of the interventricular septum, diagnosed ante mortem, following myocardial infarction, are reported. Clinical features of the disease and the available electrocardiograms with multiple chest leads are discussed. In addition, 1,292 consecutive autopsies performed at Mount Zion Hospital are reviewed, and 145 cases of recent myocardial infarction were found with eleven instances of rupture of the ventricular wall and three instances of rupture of the septum.

We are indebted to Dr. Gerson Biskind and the Department of Pathology for making the autopsy records available to us.

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A RAPID BLOOD SAMPLE COLLECTOR FOR USE IN THE DETERMINATION OF CARDIAC OUTPUT

CARL F. ROTHE, M.S., AND LEO A. SAPIRSTEIN, M.D.

COLUMBUS, OHIO

THE single injection dye dilution technique for the determination of cardiac output in man rests on sound theoretical grounds and has been empirically validated. Its usefulness is, however, somewhat limited by the difficulties attendant on collecting blood samples at one- or two-second intervals by methods originally described by Hamilton and associates.[1,2] This note describes a simple sample collector which is easily used and cleaned and which is in routine use at the University Hospital for this determination. The apparatus is constructed around a variable speed, electric drive of a Correll and Correll kymograph found in most physiology laboratories (Fig. 1). Almost any constant speed vertical drive which turns at about one revolution per minute may be used, however. A slight addition to the apparatus also permits its use as a constant infusion "pump".

METHODS

In the construction of the sample collector, fifty-three 11/32 by 1¼ inch holes with a capacity of about 2 ml. are drilled around the circumference of a Plexiglass disk (Figs. 2 and 3). The holes are spaced so that the thickness of the plastic separating the holes is about 1/16 inch. Countersinking the holes gives a beveled separation which permits excellent fractionation of the drops. A recess, machined on a lathe, is used for collecting the waste blood just before the samples are taken. The inner sides of the holes are machined lower than the partitions so that any overflow, if it occurs, goes into the recess rather than into the adjacent holes (Fig. 3). A collar with a 3/8 inch center shaft is placed on the drive shaft of the kymograph. The sample collecting disk is fastened in place with a wing nut which permits firm clamping and easy removal. The insides of the drilled collecting holes are smoothed by swabbing with a thin chloroform-Plexiglass solution.

In collecting samples, while the the disk rotates, the arterial catheter is permitted to flow into the center recess until just after the dye is injected. Its holder is then swung over the collecting holes, and sample collection is made for the required time.

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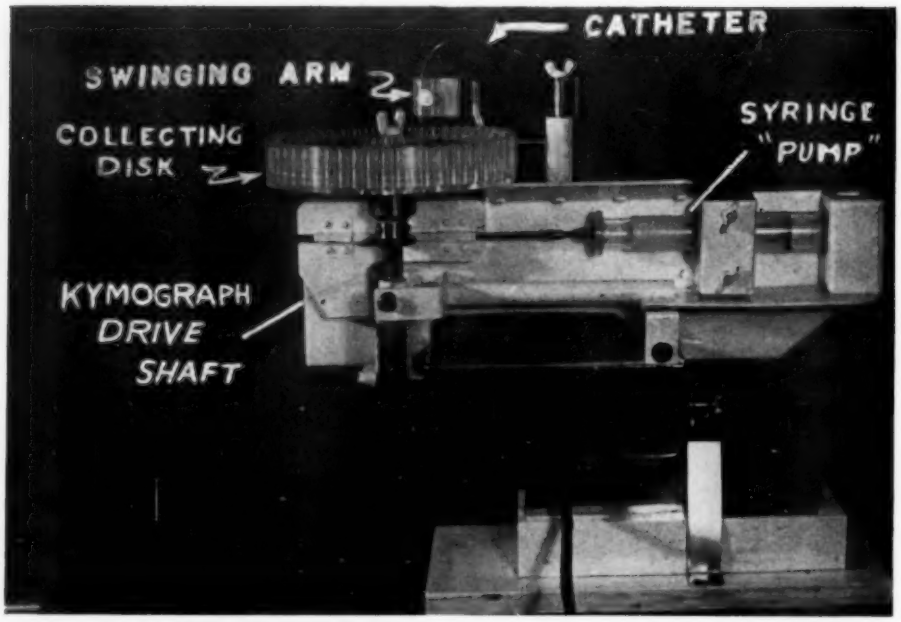

Fig. 1.—Side view of a rapid blood sample collector and a constant infusion "pump."

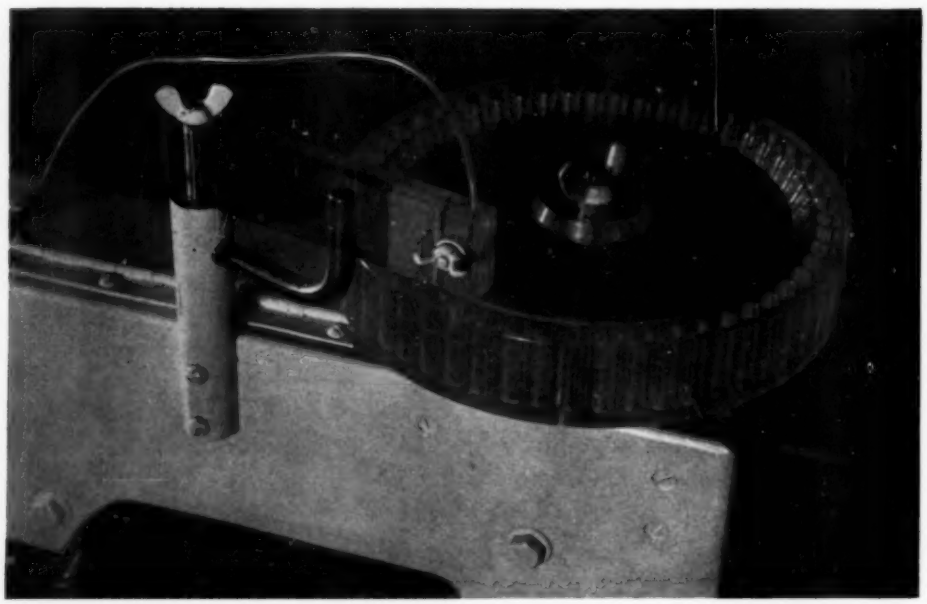

Fig. 2.—Top view of the sample collector showing the swinging catheter holder.

For the analysis, 0.2 to 0.3 ml. of blood is pipetted into 3.0 ml. of normal saline and the mixture centrifuged. The colorimetric analysis is made on the resulting supernatant liquid. This permits the direct determination of whole blood cardiac output and eliminates the need of determining the hematocrit.

Cleaning is accomplished simply by water rinsing of the whole collecting disk. Before use, the collector is heparinized by scrubbing each hole with a cotton applicator soaked in heparin. The whole process of washing, heparinizing, and drying is accomplished in 15 minutes, but may be speeded materially by air-blast drying.

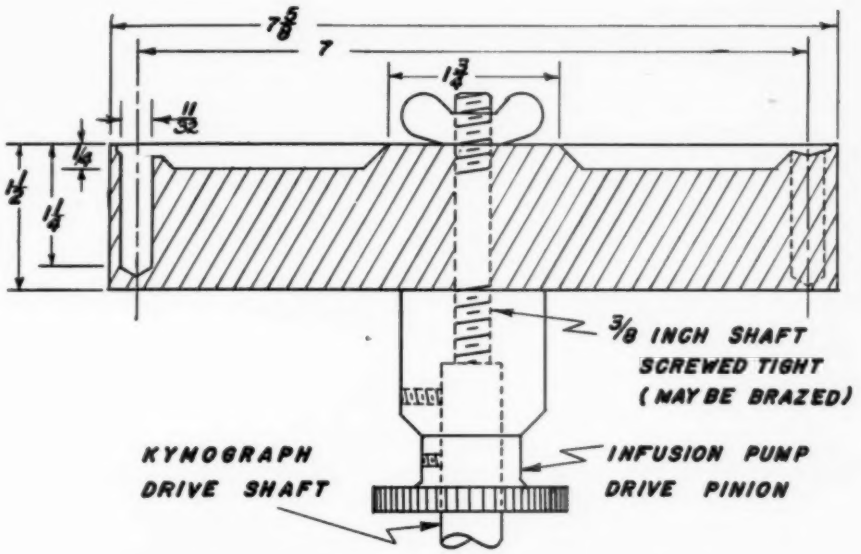

Fig. 3.—A cross-section view of the Plexiglass collecting disk.

The variable speed drive is also employed for a constant infusion, low-volume syringe type pump. A frame on which are fastened clamps for a 50 ml. syringe is fastened on one side of the kymograph drive as shown in Fig. 1. A 44-tooth pinion fastened onto the kymograph shaft drives a matched rack which drives the syringe.

RESULTS

In repeated measurements of cardiac output in man, by the dye-dilution method, it has been found that a sample collection period of two seconds makes possible the accurate construction of the dye-dilution curve. A curve obtained from a patient with toxemia of pregnancy is presented in Fig. 4. The cardiac output calculated from the curve is 4.01 liters per minute. The curves obtained are similar in all essential respects to those of Hamilton and associates.[2]

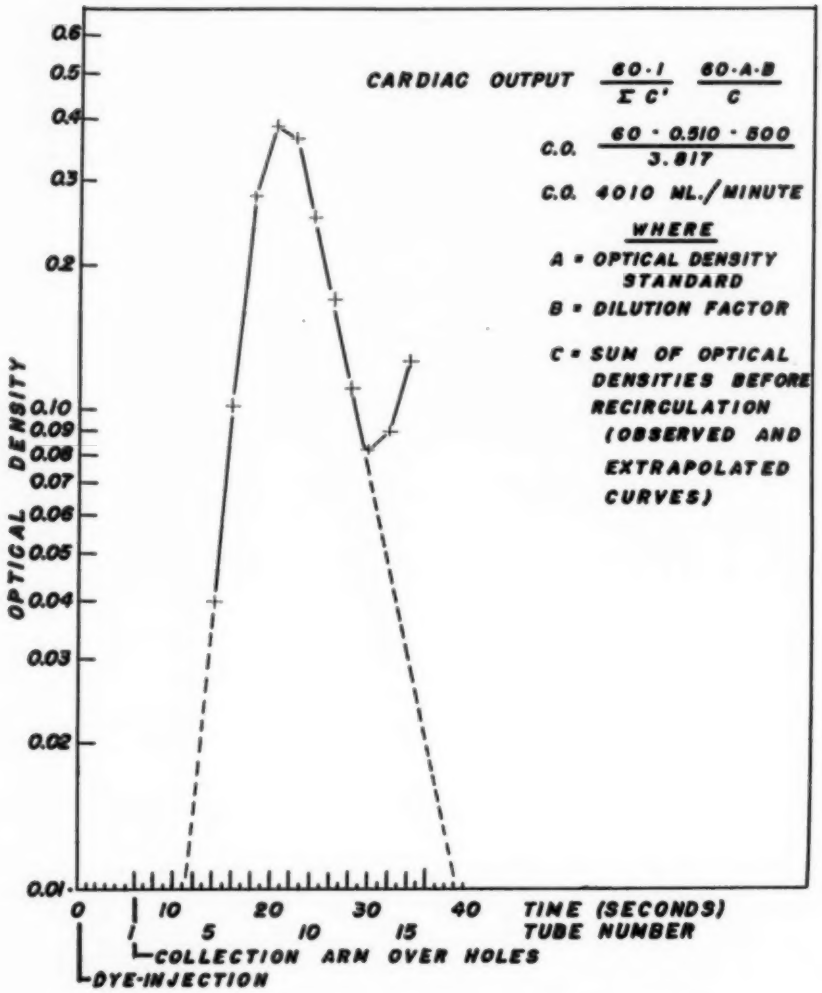

Fig. 4.—A typical dye-dilution curve for determination of cardiac output.

DISCUSSION

The outstanding advantages of this collector are the accuracy of collection and ease of cleaning in comparison to the laborious task of mounting and bridging test tubes on a kymograph drum as in the method of Hamilton and associates.[2] Blood collection begins while the disk is in motion, so that no errors associated with speed pickup are introduced. The close spacing of the holes, the beveled edges, and the use of a polyethylene collection tube placed just above the holes allow accurate fractionation of the drops during the continuous movement of the disk. The small size of the tubes permits easier and more accurate transfer of small quantities of blood.

SUMMARY

A plastic disk with appropriately spaced holes in the circumference is described for convenient collection of arterial blood samples at one- or two-second intervals for the determination of cardiac output by the dye-dilution method. A complete determination and cleaning of the apparatus may be easily completed in less than an hour.

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Clinical Reports

PULMONARY ARTERY ENLARGEMENT SIMULATING A NEOPLASM OF THE LUNG

Case Report With Angiocardiographic Studies

Theodore J. Talbot, M.D., and Jacob J. Silverman, M.D.

Staten Island, N. Y.

WITH conventional roentgenography abnormalities of the pulmonary arteries are sometimes deceiving. They may simulate among other conditions a hilar lymph node or a neoplasm. Consequently, an enlargement of the pulmonary artery may lead to grave errors of interpretation. This mistake has, in fact, led on occasions to needless surgical intervention. Since the value of angiocardiography in demonstrating a dilatation or an aneurysm of the pulmonary artery is now firmly established, this procedure is used with increasing frequency to differentiate the pulmonary artery and its branches from both vascular and nonvascular conditions of the chest. It is the purpose of this report to describe an instance of left pulmonary artery enlargement that simulated in the conventional roentgenograms of the chest a sharply demarcated mass in the hilum of the left lung indistinguishable from a neoplasm. By means of angiocardiography the differential diagnosis was established.

CASE REPORT

The patient, R.R., was a 69-year-old man who first came to our attention on June 10, 1952 because of a recent history of hemoptysis. The onset was described as sudden with expectoration of a "glassful of bright red blood." Blood streaking continued for three days, then completely subsided. He denied cough, expectoration, chest pain, breathlessness, loss of weight, fever or night sweats. He worked as a plumbing inspector and lived on Staten Island all his life.

For the past three years he had been under the care of another physician because of recurrent frontal headaches which were attributed to an elevated blood pressure. He gave a history of "pneumonia" on three occasions at the ages of 25, 35, and 65. Venereal disease was denied by name and symptom. He smoked on the average of one package of cigarettes a day. The family and marital history was noncontributory. There was no family history of cancer, tuberculosis or unusual bleeding.

On physical examination the patient's nutrition and development were good. He was symptom free and afebrile. The blood pressure in each arm averaged 200 mm. Hg systolic and 110 mm. diastolic. The heart sounds were of normal quality and regular; no murmurs were heard. The aortic second sound was accentuated. The pulse rate was 76 per minute. Examination of the chest and lungs was unremarkable. There was no abnormal dullness and expansion was

From the Medical Service of The Staten Island Hospital, Staten Island, N. Y.
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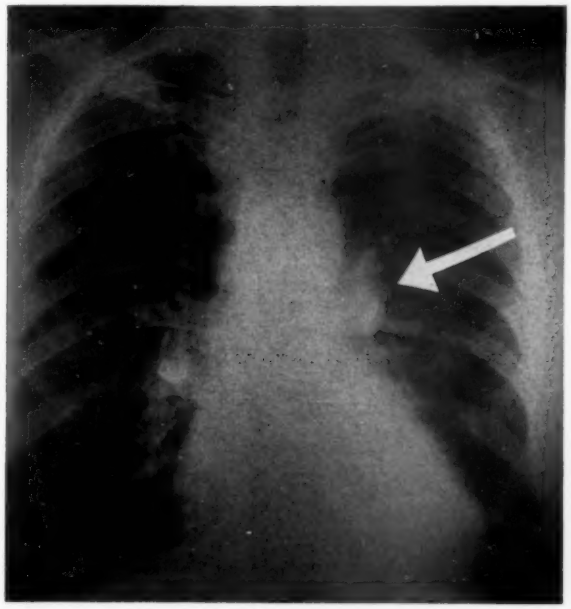

Fig. 1.—Conventional roentgenogram of chest demonstrating a mass in left hilum (arrow).

Fig. 2.—Angiocardiogram, frontal view, demonstrating prominence of left pulmonary artery (arrow) accounting for mass in left hilum of Fig. 1.

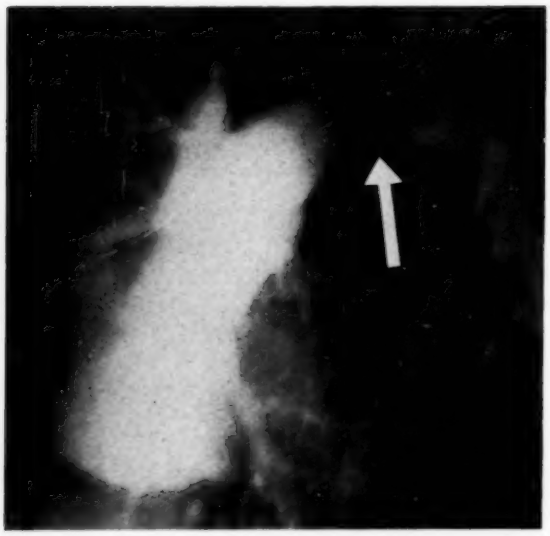

Fig. 3.—Angiocardiogram, left oblique view, demonstrating course of left pulmonary artery (arrow).

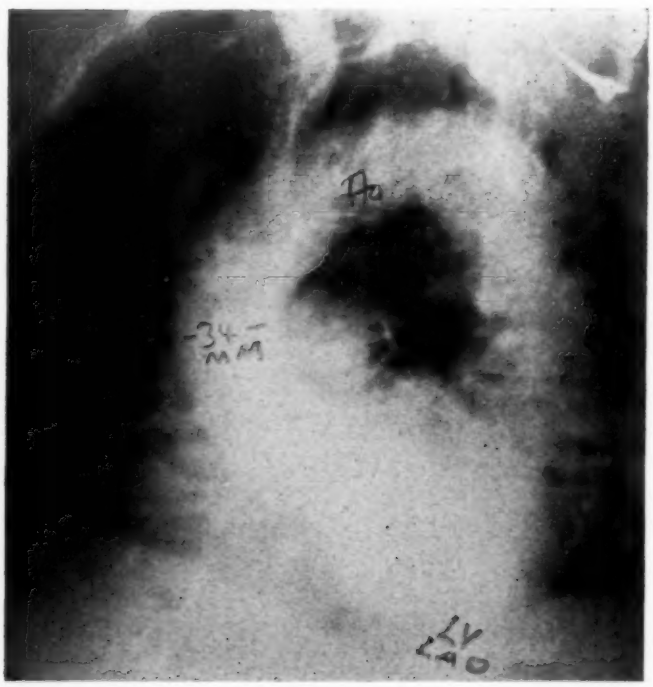

Fig. 4.—Angiocardiogram, left oblique view, demonstrating normal outline of aorta and left ventricle.

good. Auscultation of the lungs revealed normal breath sounds throughout. No râles or adventitious sounds were detected. The liver and spleen were not palpable. There was no lymphadenopathy. Digital examination of the rectum disclosed normal findings. There was no clubbing of the fingers and toes. There was no cyanosis or evidence of telangectasia of the skin or mucous membranes. Pulsations of the neck were normal. The red blood cell count was 5,790,000 per c. mm., and the hemoglobin concentration was 18 Gm. per 100 c.c. The white cell count was 7,100 per c. mm. with a normal differential count. The Kolmer serologic test for syphilis gave a 4-plus reaction; Venereal Disease Research Laboratory slide test was reported as weakly positive, undiluted. These abnormal serologic findings were confirmed on two subsequent studies. An electrocardiographic study was normal.

The conventional posteroanterior roentgenogram of the chest (Fig. 1) disclosed a semicircular tumor-like density measuring 5 cm. in its longest diameter at the level of the left hilum immediately below the left knob. With left oblique and lateral supplementary views the mass was poorly visualized. Tomographic studies were likewise disappointing. The dense shadow appeared superimposed on the hilum and could not be ascribed definitely to either an enlarged lymph node or a pathologic disturbance in the vascular or pulmonary structure. The course of the aorta, although poorly visualized, could be identified and followed throughout its course in the chest. Fluoroscopic study disclosed definite pulsations in the region of the mass. These pulsations appeared weak and seemed transmitted from neighboring vessels. A bronchoscopic examination revealed no abnormalities. Bronchoscopic washings, including special studies for tumor cells, were negative.

Because of the patient's advanced age and the history of hypertension there was hesitation to advise surgical exploration. Furthermore, since the possibility of a benign vascular shadow could not be completely excluded the patient was referred for angiocardiographic studies.* These studies (Figs. 2, 3, 4) clearly demonstrated that the mass in the left hilum represented an enlarged pulmonary artery. Prior to these studies the patient was treated with a course of 9.6 million units of penicillin. He has been followed for over a year. During this time there has been no change in the size of the mass. There has been no recurrence of hemoptysis and except for mild headaches his health has been good. Serologic studies for syphilis still show a 4-plus Kolmer reaction and a Venereal Disease Research Laboratory test weakly positive, undiluted.

DISCUSSION

Dilatation or aneurysm of the pulmonary artery is no longer considered a rare condition. The literature on this rapidly growing subject has been reviewed by Brenner,[1] Boyd and McGavack[2] and more recently by Deterling and Clagett.[3] The causes of pulmonary artery enlargement are multiple and include syphilis, mycotic infections; certain congenital anomalies, such as interauricular septal defect, patent ductus arteriosus, pulmonic stenosis, and transposition of the great vessels; mitral stenosis, a variety of chronic pulmonary diseases, thoracic deformities, pulmonary embolism, cardiac failure, and possibly hyperthyroidism, and trauma.[1-4] Pulmonary artery enlargement may also represent a normal variation. As Dotter and Steinberg[5] pointed out, it may be extremely difficult to differentiate a simple dilatation from a true aneurysm, and unless specialized studies including cardiac catheterization are performed, the true nature of the pulmonary artery enlargement may remain in doubt.

In conventional roentgenoscopy, dilatation or enlargement of the pulmonary artery is demonstrated in the frontal projection as a bulge or prominence with

*The angiocardiographic studies were performed at the New York Hospital under the direction of Dr. Israel Steinberg. Serial studies at one-second intervals were made in the frontal and moderate oblique views utilizing the Fairchild magazine.

its convexity to the left immediately beneath the aortic knob. In the oblique and lateral views dilatation of the outflow tract of the pulmonary artery may be suggested by prominence of the upper anterior cardiac border and diminished retrosternal space. An enlarged pulmonary artery also characteristically indents the esophagus. Dilatation of the left pulmonary artery is best demonstrated in the left oblique view as a dense shadow crossing the left bronchus. In this view the right branch of the pulmonary artery normally appears as a rounded area of density within the hilar shadow.

It is not sufficiently appreciated that an enlarged pulmonary artery, congenital or acquired, may be deceptive in its appearance. In our patient, for example, the circumscribed mass in the left hilum noted in the posteroanterior projectional view of the conventional roentgenogram of the chest (Fig. 1) closely resembles a primary carcinoma of the lung which had not yet infiltrated peripherally to any appreciable extent. Although a pulsation was noted in this area and suggested a vascular lesion, it was thought that the pulsation may have been transmitted from a neighboring structure. Angiocardiography, however, clearly settled the issue (Figs. 2, 3). By this technique it was shown that the circumscribed density in the left hilum was formed by an enlarged pulmonary artery which in the frontal plane was viewed on end.

Whether this enlarged pulmonary artery is an aneurysm or a simple dilatation of no clinical significance is impossible to state on the basis of our limited observations and studies. Its relationship to the hemoptysis also remains unsettled. The diagnosis of a pulmonary artery aneurysm is suggested by the finding of a positive serologic test for syphilis. The aorta, incidentally, was normal (Fig. 4). The patient has been observed for over a year and has been relatively symptom-free except for a minor episode of hemoptysis. Physical examination has been persistently negative. The symptoms and findings of pulmonary artery aneurysm, however, vary widely; it may be a surprise finding at autopsy. Regardless of the etiology, an enlarged pulmonary artery, congenital or acquired, can easily be mistaken for a neoplasm. Conversely, a pulmonary neoplasm and sometimes an aortic aneurysm have been mistaken for an enlarged pulmonary artery.[6] Obviously, angiocardiography is an invaluable medium for studying vascular shadows in or around the hilum.[5,7,8] Although not diagnostic in our patient, it should be pointed out that occasionally laminographic studies will clearly delineate anomalous pulmonary vessels. We recently reported a patient, surgically cured, in whom a benign appearing shadow in the pulmonary parenchyma masqueraded as a neoplasm. Prior to operation tomograms demonstrated two major vessels extending from the hilar region which proved to be an arteriovenous fistula of the lung.[9]

SUMMARY

An unusual enlargement of the left branch of the pulmonary artery is reported in a 68-year-old man that closely simulated a neoplasm of the lung. Angiocardiography was successful in establishing the correct diagnosis.

With conventional roentgenography vascular shadows may be encountered in either hilum that are difficult, if not impossible, to differentiate from a neoplasm. Angiocardiography is ideally suited for identifying these shadows.

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ATRIAL FLUTTER: 1 TO 1 CONDUCTION DURING TREATMENT WITH QUINIDINE AND DIGITALIS

FRANK LONDON, M.D.,* AND MILTON HOWELL, M.D.**

BETHESDA, MD.

INTRODUCTION

ATRIAL flutter is an uncommon cardiac arrhythmia found in less than 0.2 per cent of patients clinically suspected of having heart disease.[1,2] Its manifestations are, in large part, dependent on the accompanying ventricular rate. Usually some degree of auriculoventricular block is present, resulting in a ventricular rate slower than the atrial rate. Occasionally, however, the ventricular rate rises to the level of the atrial rate. Persistence of such rapid ventricular rates, particularly in the presence of heart disease, is almost invariably associated with syncope, circulatory collapse, or pulmonary congestion.

A survey of the reported cases of atrial flutter reveals that the development of 1 to 1 conduction is usually associated with quinidine therapy, exercise, or emotional disturbances. Because of the possibility of 1 to 1 conduction developing in patients with atrial flutter being treated with quinidine it has become common practice[3,4] to precede quinidine therapy in this condition with digitalis. This use of digitalis is entirely apart from its known effect in eradicating atrial flutter and is based on the fact that it decreases the conduction rate of the auriculoventricular node and tends to "fix" the heart block.

That digitalis will not always prevent 1 to 1 conduction in atrial flutter during treatment with quinidine is becoming increasingly clear. Four patients have been reported[6,7] previously in whom this type of conduction developed on quinidine therapy despite the concomitant use of digitalis. One patient has also been reported[8] who developed 1 to 1 conduction while on treatment with procaine amide and digitalis. The amounts of digitalis given to these five patients is not clear from the reports.

The purpose of this paper is to report a patient with atrial flutter who developed repeated episodes of 1 to 1 conduction associated with serious symptoms while being treated with quinidine and adequate amounts of digitalis.

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*The Clinic of General Medicine and Experimental Therapeutics, National Heart Institute, Bethesda, Md.

**United States Public Health Service Hospital, Baltimore, Md.

CASE REPORT

A 64-year-old Negro entered the United States Public Health Service Hospital, Baltimore, Md., on April 12, 1953, complaining of dizziness, shortness of breath, burning substernal pain, and weakness of six days' duration. The past history revealed that he had been well except for intermittent claudication and mild pedal edema for six months prior to admission.

Physical examination revealed a Negro in moderate respiratory distress. The blood pressure 150/100 mm. Hg; the pulse rate was 136; and the respiratory rate was 40. There was moderate sclerosis of the retinal vessels. There were moist inspiratory râles at both lung bases. The heart was thought to be enlarged by percussion. There was moderate pitting edema of both ankles. The remainder of the examination revealed no significant abnormality.

The admission blood count, urinalysis, and blood chemistry examinations were all normal. The chest roentgenogram showed cardiac enlargement and pulmonary congestion. An electrocardiogram taken on admission (Fig. 1,*A*) showed atrial flutter with 2:1 atrioventricular block and an atrial rate of about 270.

Shortly after admission the patient was started on treatment with mercurial diuretics, aminophylline, and Cedilanid (1.6 mg. intravenously). A rapid diuresis with clearing of the pulmonary râles occurred, but the substernal pain and rapid pulse continued.

Six hours after admission 0.3 mg. of digitoxin was given orally, and quinidine therapy was instituted. A test dose of 0.2 Gm. of oral quinidine sulfate was given and this was followed by doses of 0.4 Gm. at intervals of two hours. One hour after the third dose, (total 1.0 Gm.), the patient developed severe substernal pain and signs of collapse. The electrocardiographic tracing at this time superficially resembled ventricular tachycardia (Fig. 1,*B*). Carotid sinus pressure immediately produced a constant 2:1 atrioventricular block revealing the previous arrhythmia as auricular flutter with 1 to 1 conduction (Fig. 1,*C*).

At this point 0.6 mg. digitoxin was administered intravenously to insure adequate digitalization, and after waiting six hours quinidine therapy was resumed. Three doses, each of 0.4 Gm. quinidine sulfate intramuscularly, followed by two doses each of 0.6 Gm. quinidine sulfate intramuscularly at two-hour intervals, resulted in a second occurrence of 1 to 1 conduction (Fig. 1,*D*). The total amount of quinidine given up to this time was 3.4 Gm. Carotid sinus pressure again reduced the ventricular rate promptly. The patient was immediately relieved of the substernal pain and signs of syncope. Quinidine was discontinued after two additional doses of 0.6 Gm. each because of nausea and frequent ventricular premature contractions. After another 0.6 mg. of digitoxin the patient was then treated with a low-salt diet and 0.2 mg. digitoxin daily for six days. During this time the atrial flutter with 2 to 1 conduction persisted.

On the seventh day reversion was again attempted. Quinidine sulfate 0.6 Gm. was given orally at intervals of two hours. An hour after the fourth dose (total 2.4 Gm.) the patient arose from bed to use the urinal and developed sudden onset of severe substernal pain, dizziness, and weakness. The pulse was not obtainable. The electrocardiogram (Fig. 1,*E*) again showed atrial flutter with 1 to 1 conduction. Carotid sinus pressure stopped the 1 to 1 conduction and restored a 2 to 1 atrioventricular block (Fig. 1,*F*). The patient's condition improved rapidly, and quinidine was discontinued.

The patient was discharged on the thirty-first hospital day, taking 0.1 mg. digitoxin daily. Flutter persisted at this time with a varying 3 to 1 and 4 to 1 atrioventricular block. Fourteen days after discharge on his return to the Outpatient Department, his pulse was found to be regular. The electrocardiographic tracing showed that he had reverted to normal sinus rhythm at some time following discharge from the hospital (Fig. 1,*G*).

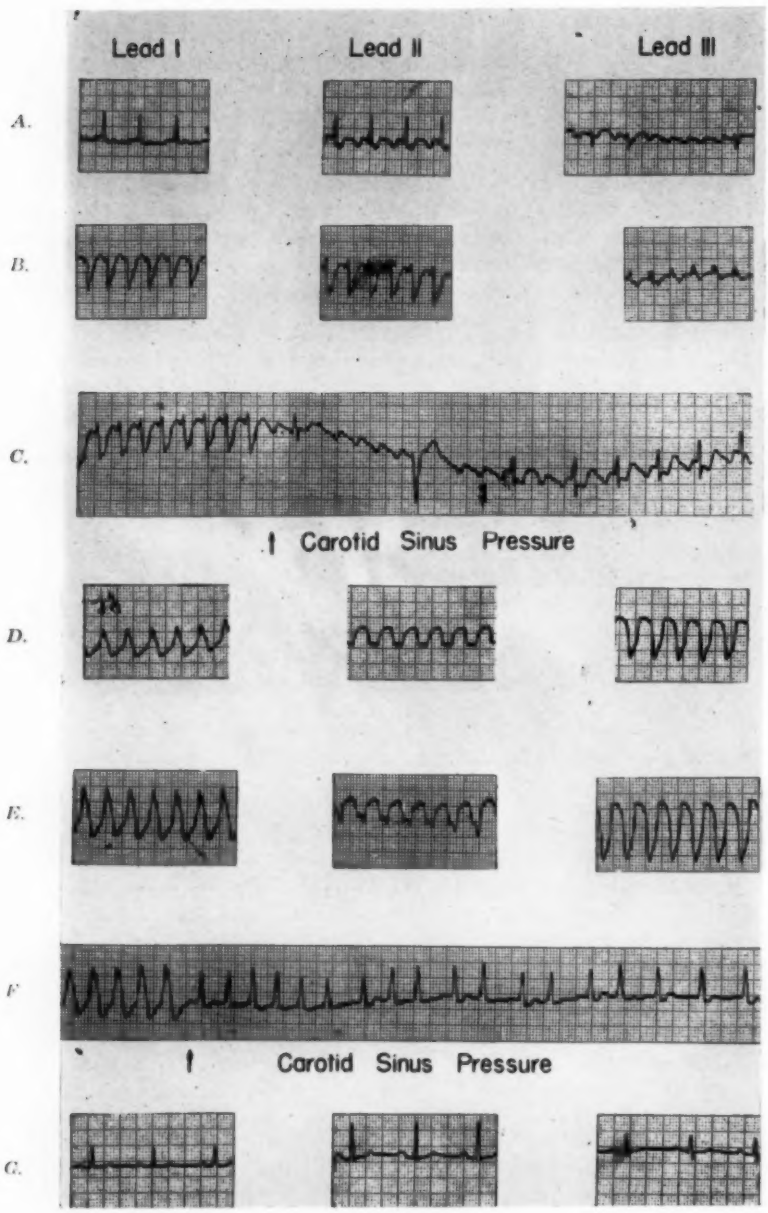

Fig. 1.—*A*, Electrocardiogram on admission. Atrial flutter with 2 to 1 block. *B*, Electrocardiogram twelve hours after admission. Atrial flutter with 1 to 1 conduction. *C*, Reversion of 1 to 1 conduction to 2 to 1 conduction with carotid sinus pressure. *D*, 24 hours after admission. Atrial flutter with 1 to 1 conduction again induced by quinidine. *E*, 7 days after admission. *F*, Conversion of atrial flutter from 1 to 1 conduction again by carotid sinus pressure. *G*, Electrocardiogram after reversion to regular rhythm.

DISCUSSION

Jolly and Ritchie[9] discussed atrial flutter in 1910, and in 1914 Ritchie[10] published a monograph which established the clinical features of this arrhythmia. This work, together with the experimental investigations of Lewis,[11] in which he postulated a circus mechanism in the atrial musculature as the basis for the arrhythmia, led to the general acceptance of atrial flutter as a physiologic and clinical entity. The introduction of new experimental methods for the production of atrial arrhythmias by Scherf[12] and by Rosenblueth and Garcia Ramos[13] in 1947 led to a resurgence of interest in these conditions. The comprehensive investigations of Prinzmetal and his group[14] utilizing Scherf's aconitine method and newer techniques of photography and electrocardiography suggested that all of the atrial arrhythmias may arise from a single tachysystolic focus. This constitutes a serious challenge to the theories of Lewis. This controversy notwithstanding, these investigators agree that there are clinical, therapeutic, and electrocardiographic dissimilarities between atrial flutter and paroxysmal atrial tachycardia.* The case reported herein would seem to conform well with the accepted criteria for the diagnosis of atrial flutter.

The development of 1 to 1 conduction in atrial flutter is uncommon but in an incomplete review of the literature we were able to find thirty-one cases reported. Some approximation of the incidence of this complication can be derived from the fact that in the three largest series of patients[2,4,16,17] eleven out of approximately two hundred patients developed this complication. The symptoms of atrial flutter with 1 to 1 conduction may resemble those of myocardial infarction, cerebrovascular accidents, pulmonary edema, or shock. The electrocardiographic diagnosis is frequently complicated by the development of aberrant ventricular conduction. The widened abnormal QRS complexes may be easily confused with those of ventricular tachycardia. Under these circumstances carotid sinus pressure may be of extreme diagnostic and therapeutic value because it frequently induces some degree of auriculoventricular block. The value of carotid sinus pressure is illustrated by the fact that it immediately terminated each of three episodes of 1 to 1 conduction experienced by our patient.

The first episode of 1 to 1 conduction after 1.6 mg. Cedilanid and 0.3 mg. digitoxin, the second episode after the Cedilanid and 0.9 mg. digitoxin, and the third episode after 1.5 mg. digitoxin in 24 hours, and 0.2 mg. daily for 5 days, make it clear that adequate doses of digitalis will not always combat the tendency toward 1 to 1 conduction that develops in patients with atrial flutter treated with quinidine.

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*The authors prefer the term atrial flutter to paroxysmal auricular tachycardia with 2 to 1 block. We believe that Prinzmetal has demonstrated the artificialities which have been used to distinguish the two. It is to be hoped a more physiologic terminology for atrial arrhythmias will come into general use.

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ACCELERATED AURICULOVENTRICULAR NODAL CONDUCTION AS A TRANSITORY PHENOMENON IN A NERVOUS PATIENT

RUSTOM JAL VAKIL, M.D.(LOND.), M.R.C.P.(LOND.), D.T.M.&H. (LOND.), F.R.F.P.S.G., F.C.P.S., F.A.SC.

BOMBAY, INDIA

IN view of certain remarkable electrocardiographic features, the following case report is considered worthy of publication.

CASE REPORT

A 60-year-old Parsee man, of sedentary habits and no occupation, has been periodically observed, during the last few months for nervous depression and "fear of heart disease." Apart from a few childhood ailments, he has always been remarkably healthy, never having had chest pain, dyspnea, edema, vertigo, or symptoms suggestive of organic disease.

On examination, he is a moderately well-developed and well-nourished man, with no evidences of clubbing, cyanosis, or anemia. The apex impulse is seen and felt in the fifth left intercostal space, 1 cm. inside the mid-clavicular line. The heart appears normal on percussion and auscultation. The pulse rate usually varies between 70 and 90 per minute and the blood pressure between 140 and 155 mm. Hg systolic and 80 to 90 mm. diastolic. At no time, has he had symptoms or signs of myocardial insufficiency or infarction. On fluoroscopy, the heart and aorta appear normal and the lung fields clear.

On many an occasion, the patient has had routine electrocardiograms, usually at his own bidding. Fig. 1, *A* represents his normal electrocardiogram. It shows a cardiac rate of 84 beats per minute, the P wave is upright and of normal height and duration, the P-R interval is normal and measures 0.16 sec. and the QRS complex and S-T-T segment are normal in all respects.

On one occasion, during a particularly bad nervous spell accompanied by considerable emotional disturbance, vasomotor flushing, and an acute "fear of heart failure," the patient's electrocardiogram (Fig. 1,*B*) showed a somewhat different picture. In spite of the QRS complex and S-T-T segments being no different from those in the previous tracings, the cardiac rate was higher (110 beats per minute), the P wave duration shorter, and the P-R interval reduced to 0.08 sec., or exactly one-half of its previous value.

After a dose of sedative mixture, rest in bed, and some degree of reassurance, the electrocardiogram which was repeated after a few hours showed a reversion to the normal type (Fig. 1, *A*).

Since that time, the electrocardiogram has been taken on several occasions, but the short P-R interval has not returned.

From the Cardiological Department, King Edward Memorial Hospital, Bombay, India.

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DISCUSSION

During routine electrocardiography, in a perfectly healthy but hypersensitive individual of 60 years, the following electrocardiographic abnormalities were noted, as a transitory event, for a few hours, during a particularly severe nervous spell, namely, (1) a shortening of the P-R interval from 0.16 sec. to 0.08 sec.;

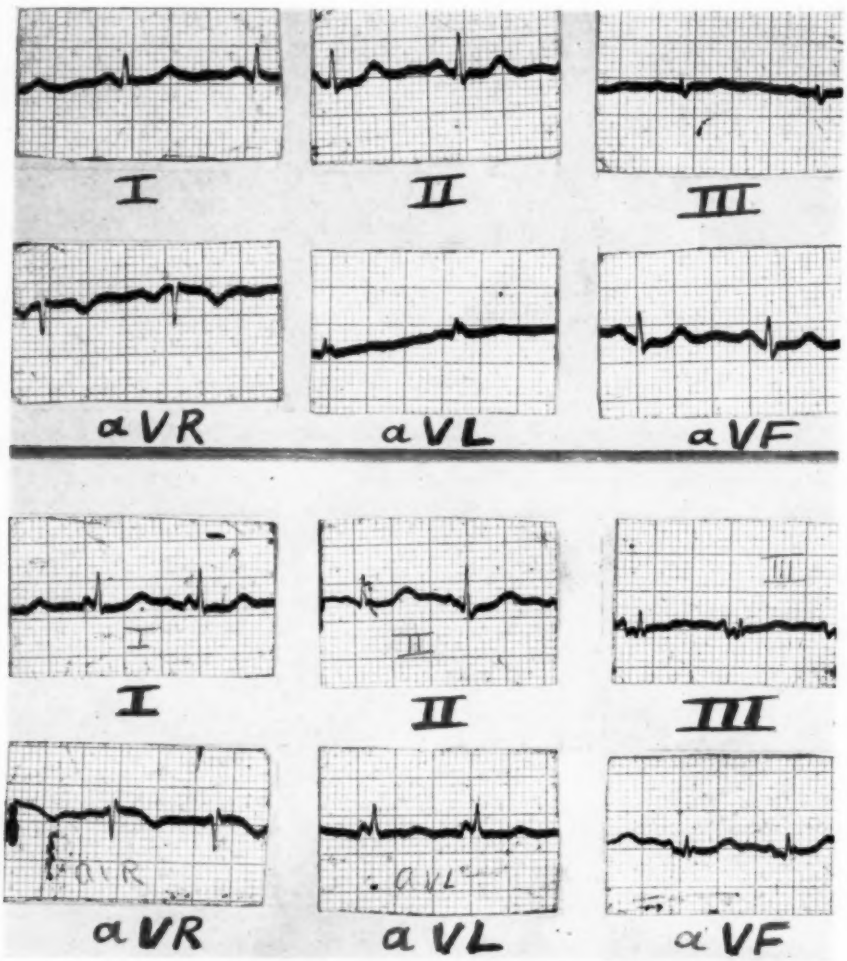

Fig. 1.—Electrocardiograms showing the standard and unipolar extremity leads. *A*, Control or standard electrocardiogram of patient, with a normal P-R interval (0.16 sec.); *B*, Abnormal electrocardiogram obtained on one occasion only, with a short P-R interval (0.08 sec.), a shorter duration of the P wave and sinus tachycardia (110 beats per minute).

(2) a reduction in the duration or width of the P wave; and (3) sinus tachycardia (a rate of 110 beats per minute instead of his customary rate of 70 to 90 beats per minute).

The syndrome of normal and upright P waves with shortening of P-R interval to 0.12 sec. or less has been discussed at length in the literature and several

different mechanisms have been incriminated in its production, namely, (1) myocardial infarction or damage, usually of posterior wall type;[4,8,12] (2) hypertension, particularly during left ventricular strain;[4,10,11] (3) vitamin B_1 deficiency;[10,11] (4) coronary sinus rhythm or coronary type of auriculoventricular nodal rhythm;[3,10] (5) the "pre-excitation" or Wolff-Parkinson-White syndrome;[13] (6) delayed sinoatrial with normal sinoventricular conduction;[4,12] and (7) increased conduction velocity through the atrioventricular node or so-called accelerated nodal conduction from thyrotoxicosis or sympathetic stimulation.[4]

Each of these mechanisms was considered separately, in connection with the present case.

Shortening of the P-R interval has been reported in many cases of acute myocardial infarction[4,8,12] and attributed to delayed sinoatrial with normal sinoventricular conduction.[4] Prinzmetal and associates[8] have reported the Wolff-Parkinson-White syndrome after myocardial infarction of posterior wall type and in other pathologic lesions involving the auriculoventricular node. In their opinion,[8] the abnormal beats, in such cases, are examples of acquired acclerated conduction beats of nodal origin. Shortening of the P-R interval has been repeatedly reported in cases of hypertension,[4,10,11] particularly after the inception of left ventricular failure.[10,11] The mechanism of the shortening, in such cases, remains obscure.[4] Shortening of the P-R has also been described in cases of vitamin B_1 deficiency.[10,11] In view of the fact, that this patient has never displayed any symptoms or signs of myocardial damage, infarction, hypertension, left ventricular strain, or vitamin deficiency, these possibilities can be ruled out and more so, in view of the evanescent nature of the electrocardiographic abnormality.

Coronary sinus rhythm[3] is a condition characterized by upright P waves in Leads I and II and a short P-R interval, 0.02 to 0.10 sec. in duration. The impulse, in such cases, is supposed to arise close to the caudal end of the sinoauricular node and, hence, behaves like an impulse of sinus origin. Of late, Scherf[10] has denied the atrioventricular nodal origin of this electrocardiographic entity. He regards it as a sinus rhythm with a pathologically shortened P-R interval. In the present case, the entity of coronary sinus rhythm is ruled out by the paradoxical rise in the rate of cardiac beating during the P-R shortening, by the absence of all evidence of organic heart disease, and by the evanescent nature of the anomaly.

Rare cases of the Wolff-Parkinson-White syndrome[13] are on record, where the characteristic widening of the QRS complex is absent or insignificant. Fox[2] and Burch and Kimball[1] have described cases with slurred QRS complexes of normal width, while Lown and associates[5] and Burch and Kimball[1] have reported cases with perfectly normal QRS complexes. Even assuming the existence of normal QRS complexes in rare cases of the Wolff-Parkinson-White syndrome, several objections can be raised against the present case being one of this syndrome, namely, (1) the age of the patient, (2) no history of paroxysmal tachycardia at any time, and (3) the absence of similar P-R shortening, at any time, in the past or present.

Since the mechanism of delayed sinoatrial conduction implies a state of myocardial infarction or damage, it can be ruled out.

In our opinion, the only possible explanation for the electrocardiographic abnormality of the present case, is one of sympathetic stimulation,[4] resulting in accelerated nodal conduction or increased conduction velocity through the atrioventricular node. In favor of this contention, the following arguments can be put forward, namely, (1) the complete absence of all evidence of organic heart disease, clinically, fluoroscopically and electrocardiographically; (2) the transitory or evanescent nature of the electrocardiographic finding; (3) clinical evidence of an acute emotional disturbance during the taking of the abnormal tracing; (4) the coexisting abnormalities of sinus tachycardia and narrow P waves, both confirmatory of sympathetic stimulation; and (5) numerous clinical and experimental observations, reported in the literature from time to time. According to Lepeschkin,[4] stimulation of the sympathetic nerves leads to P-R interval shortening, together with increase in amplitude and decrease in duration of the P waves. These abnormalities are ascribed to an increased velocity of conduction. Epinephrine has been shown to cause tachycardia with shortening of P-R interval and QRS duration.[4] In mental cases, a shortened P-R interval, below 0.12 sec., is said to be thirty times as common as in normal subjects, and is said to return towards normal with improvement in the mental condition of the patient.[4,6,9]

By assuming, then, this theory of sympathetic overstimulation, with resultant acceleration of atrioventricular nodal conduction, the actual degree of the latter defect can be calculated, for the present case, by the semiquantitative method of Prinzmetal and associates.[8] If acceptance is made of 0.07 sec. as the time required for the impulse to travel from the sinoauricular node to the atrioventricular node, it can be deduced by simple calculation that the impulse delay at the atrioventricular node in this case dropped from 0.09 sec. (with a P-R of 0.16 sec.) to 0.01 sec. (with a P-R of 0.08 sec.) during the phase of electrocardiographic abnormality.

SUMMARY

An unusual case is described, of a normal, healthy man of 60 years, with a transitory shortening of the P-R interval to one-half its normal value during a phase of acute emotional disturbance.

After evaluation of the various possible mechanisms for such an electrocardiographic abnormality, the theory of sympathetic stimulation resulting in accelerated atrioventricular nodal conduction is put forward as the most likely explanation.

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Book Reviews

A Manual on Cardiac Resuscitation. By Robert M. Hosler, M.D., 183 pages, Springfield, Ill., 1954, Charles C Thomas Company

Cardiac arrest or ventricular fibrillation is a disastrous complication which can occur in any surgical operation and is now appearing with such frequency that it should be of great concern to all surgeons and anesthesiologists. These catastrophes occur not only in persons who are being operated upon for cardiovascular disease (under which circumstances the surgeon is generally prepared to deal with the problem promptly and efficiently), but they are plaguing most clinics and operators who encounter sudden cardiac stoppage during general operations on patients who were believed to have normal hearts. This loss of life in subjects who were thought to be good operative risks has reached appalling numbers.

This timely manual by Dr. Hosler calls attention to the problem of cardiac arrest which appears during surgery, summarizes the causes of such disasters, and indicates the manner in which arrests can be prevented or reduced in frequency. The main part of the booklet is concerned with a concise and clear enumeration and discussion of the steps which must be instituted promptly if a patient is to be brought back to life and at the same time be protected from damage of the brain. Like fire drills, methods of cardiac resuscitation must be practiced before disaster strikes. All anesthetists and surgeons should be familiar with the important steps which are essential for treating patients who have suddenly had cessation of the heart beat or who have developed ventricular fibrillation. This treatise by Dr. Hosler indicates in a clear manner the techniques, the drugs, and the managements which have been found to be of value in restoring life and re-establishing effective and spontaneous beating of the heart.

R. E. G.

Practical Electrocardiography. By H. J. L. Marriott. 159 pages. Baltimore, 1954, Williams and Wilkins Company.

In the preface the author states that books on electrocardiography possess one or more disadvantages for the beginner; ". . . the introductory chapters on electrophysiology are so intricate and long-winded that the reader's interest is early drowned in a troubled sea of vectors, axes, and gradients, or certain aspects of the subject are omitted." This is undoubtedly true. He has set out to write a book of small size for students and beginners in which electrocardiographic interpretation is explained simply and yet adequately. He has succeeded admirably. All the common types of electrocardiographic abnormalities are presented and explained in a clear manner. The tracings which illustrate them are excellent and are on the same page as the text thus obviating the need of turning over several pages to find the appropriate illustrations.

There is only a limited amount of theoretical discussion, and this is clearly presented. In the reviewer's opinion this is one of the best books for beginners that has appeared since Lewis' small book. When the student has comprehended all that is contained in this volume he has a sound foundation in electrocardiography. Should he desire to delve further he can study more intelligently one of the larger textbooks which deal more exhaustively with the subject.

The book can be thoroughly recommended to students and general practitioners who desire a knowledge of the fundamental principles of electrocardiographic interpretation.

J. H. C.